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# **FDA Briefing Document**

## **Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee**

**October 16, 2014**

**Chantix and Serious Neuropsychiatric Adverse Events**

## **DISCLAIMER STATEMENT**

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought varenicline and the risk of serious neuropsychiatric adverse events to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

**Food and Drug Administration  
Center for Drug Evaluation and Research**

*Joint Meeting of the Psychopharmacologic Drugs Advisory Committee  
and Drug Safety and Risk Management Advisory Committee*

**Chantix and Serious Neuropsychiatric Adverse Events**

October 16, 2014

**Briefing Materials**

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**Food and Drug Administration**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**Division of Anesthesia, Analgesia, and Addiction Products**

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MEMORANDUM

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Date: September 22, 2014

From: Rigoberto Roca, MD  
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Division of Anesthesia, Analgesia, and Addiction Products  
Office of Drug Evaluation II, CDER, FDA

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To: Chair, Members, and Invited Guests

Re: Overview of the October 16, 2014 Joint Meeting of the Psychopharmacologic  
Drugs Advisory Committee and Drug Safety and Risk Management Advisory  
Committee Meeting

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In April 2014, Pfizer submitted a labeling supplement for varenicline (Chantix, NDA 21-928) proposing changes to the varenicline labeling relating to the risk of serious neuropsychiatric adverse events. In the cover letter of this supplement, Pfizer asserted that, "...since 2009, more reliable data on the NPS [neuropsychiatric] safety of Chantix have become available, including meta-analyses of placebo-controlled clinical trials and data from observational studies comparing varenicline to other smoking cessation pharmacotherapies. As presented in this submission, these data do not support an association between treatment with Chantix and serious NPS [neuropsychiatric] events."

Based on Pfizer-conducted meta-analyses of randomized controlled trials of varenicline and a Pfizer-conducted review of five publications of observational studies of patients treated with varenicline compared to patients treated with nicotine replacement therapy (NRT) or bupropion, Pfizer proposed implementing the following major changes to the varenicline labeling (see Attachment 9 for the specific Pfizer-proposed changes):

- Highlights of Prescribing Information:
  - Remove Boxed Warning on Serious Neuropsychiatric Events
  - Under Warnings and Precautions, add a Warning on Serious Neuropsychiatric Events in bolded font
- BOXED WARNING section of the Full Prescribing Information (FPI):
  - Remove the box (i.e., remove the single black line) around the Warning on Serious Neuropsychiatric Events and add summaries of information from neuropsychiatric meta-analyses of clinical trial data and observational studies
- WARNINGS AND PRECAUTIONS section of the FPI
  - In section 5.1 WARNINGS AND PRECAUTIONS / Neuropsychiatric Symptoms and Suicidality, add information from neuropsychiatric meta-analyses of clinical trial data and observational studies

The original signal for serious neuropsychiatric adverse events came from cases reported to the FDA and described in the medical literature. In this supplement, Pfizer contends that the information garnered from the meta-analyses they conducted and the published observational studies they have reviewed is reassuring and trumps the information culled from the case reports that originally led to the Boxed Warning and Warnings and Precautions statements in varenicline labeling, and that the sum of this new evidence no longer supports the need for a boxed warning for serious neuropsychiatric adverse events.

As summarized in the reviews included in this briefing package, the Agency's review team, including statisticians and epidemiologists, evaluated the validity of the findings from Pfizer's meta-analyses and the published observational studies. The limitations of the findings described in each of the reviews raise questions as to how to best interpret the findings of the meta-analyses and observational studies.

Based on FDA's review of the meta-analyses and observational studies submitted by Pfizer, FDA has determined that some information about these data could be included in the varenicline labeling (Attachment 10, section 5.1), in order for prescribers to have a full picture of what analyses and studies have been conducted to enhance the understanding of varenicline-associated serious neuropsychiatric adverse events.

However, the determination of whether to remove a boxed warning is a decision for which there is limited precedent. FDA believes that the randomized controlled trial prospectively designed to evaluate the risk of serious neuropsychiatric adverse events with varenicline, whose final study report is expected in a year, should be reviewed and considered as part of such a regulatory action. However, because Pfizer believes the collection of observational and meta-analytic data are alone sufficient, we are bringing this issue to the Committee for discussion.

The Division and Agency are grateful for your participation in this important meeting and for providing your expertise and insight. We thank you in advance for your advice which will assist us in determining how the new evidence effects the understanding of the risk of serious neuropsychiatric adverse events with varenicline, and how that may be communicated in labeling.

Draft Topics for Discussion:

1. What conclusions can be drawn about the risk of serious neuropsychiatric adverse events with varenicline from the meta-analysis results?
2. What conclusions can be drawn about the risk of serious neuropsychiatric adverse events with varenicline from the observational studies?
3. How do the meta-analyses and observational studies help in your understanding of the risk of serious neuropsychiatric adverse events with varenicline?
4. Based on the data presented on the risk of serious neuropsychiatric adverse events with varenicline, what would you recommend:
  - a) Removal of the boxed warning?
  - b) Modification of the language in the boxed warning?
  - c) Wait until the completion of the postmarketing randomized controlled trial to reassess the need for the boxed warning?

Please explain the rationale for your answer, and discuss any additional actions you think the Agency should take regarding the risk of serious neuropsychiatric adverse events with varenicline.

# **Varenicline and the Risk of Serious Neuropsychiatric Adverse Events**

**October 16, 2014**

## **Integrated Summary Memorandum**

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## Introduction

Varenicline, a partial  $\alpha 4\beta 2$  acetylcholine nicotinic receptor agonist, was approved in May 2006 in the United States “as an aid to smoking cessation treatment.” Varenicline’s approval was based on six placebo- and active-controlled trials of 6 to 12 weeks duration in over 3500 chronic cigarette smokers (average 21 cigarettes per day and average smoking history of 25 years).

Varenicline’s original approved labeling included a listing of the following neuropsychiatric adverse events in the ADVERSE REACTIONS section: insomnia, abnormal dreams, and nightmares. As information about serious neuropsychiatric adverse events emerged in the postmarketing period, the varenicline labeling evolved to incorporate this information:

- January 2008: Based on data from spontaneous postmarketing reports of serious neuropsychiatric adverse events, FDA determined that varenicline was associated with serious neuropsychiatric adverse events including suicidal ideation, suicidal behavior, changes in behavior, agitation, depressed mood, and worsening of preexisting psychiatric illness. A new warning was added to the WARNINGS section describing these serious neuropsychiatric adverse events; and recommendations were added for patients, their families, and caregivers to monitor for these serious neuropsychiatric adverse events during varenicline treatment.
- May 2008: FDA utilized two postmarketing safety authorities acquired under the FDA Amendments Act of 2007. FDA required Pfizer to implement a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of varenicline as an aid to smoking cessation outweighed its risk of serious neuropsychiatric adverse events. The REMS required a Medication Guide to ensure varenicline-treated patients are aware of the risk of serious neuropsychiatric adverse events. Additionally, FDA issued a postmarketing requirement (PMR) to Pfizer to conduct a randomized controlled trial to assess the risk of serious neuropsychiatric adverse events with varenicline.
- July 2009: A BOXED WARNING section was added to the varenicline labeling that described information already included in the WARNINGS section concerning the serious neuropsychiatric adverse events and recommendations to patients and their caregivers to discontinue varenicline if these serious neuropsychiatric adverse events occurred. Furthermore, the WARNINGS section was updated to include additional varenicline-associated serious neuropsychiatric adverse events including hostility, mania, psychosis, hallucinations, and paranoia.

In April 2014, Pfizer submitted a labeling supplement for varenicline (Chantix, NDA 21-928) proposing changes to the varenicline labeling relating to the risk of serious neuropsychiatric adverse events. In the cover letter of this supplement, Pfizer asserts that, “...since 2009, more reliable data on the NPS [neuropsychiatric] safety of Chantix have become available, including meta-analyses of placebo-controlled clinical trials and data

from observational studies comparing varenicline to other smoking cessation pharmacotherapies. As presented in this submission, these data do not support an association between treatment with Chantix and serious NPS [neuropsychiatric] events.”

Based on Pfizer-conducted meta-analyses of randomized controlled trials of varenicline and a Pfizer-conducted review of five publications of observational studies of patients treated with varenicline compared to patients treated with nicotine replacement therapy (NRT) or bupropion, Pfizer proposed the following major changes to the varenicline labeling:

- Highlights of Prescribing Information:
  - Remove Boxed Warning on Serious Neuropsychiatric Events
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- **BOXED WARNING** section of the Full Prescribing Information (FPI):
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- **WARNINGS AND PRECAUTIONS** section of the FPI
  - In section 5.1 **WARNINGS AND PRECAUTIONS / Neuropsychiatric Symptoms and Suicidality**, add information from neuropsychiatric meta-analyses of clinical trial data and observational studies

In the subsequent sections of this briefing document, the following is provided:

- Regulatory history leading to the boxed warning, REMS, and PMR for serious neuropsychiatric adverse events;
- Regulatory requirements and guidance recommendations for **BOXED WARNING** section and other relevant sections of the labeling;
- Utilization data for varenicline and other smoking cessation treatments;
- Update on neuropsychiatric adverse events reported to FAERS;
- Summary of FDA review of epidemiological studies cited by Pfizer; and
- Summary of FDA review of RCT meta-analyses submitted by Pfizer

## Regulatory History

Chantix® (varenicline) is a partial  $\alpha 4\beta 2$  acetylcholine nicotinic receptor agonist approved in May 2006 as an aid to smoking cessation. The treatment regimen is 1 mg twice daily for 12 weeks (with an initial one-week titration). A second 12-week course may be taken to increase the chance of maintenance of abstinence.

In May 2007, the European Medicines Agency (EMA- previously, EMEA) informed FDA that they were investigating a signal of suicidality-related adverse events. A chronology of the subsequent regulatory actions and public communications that followed is shown below.

May 2006	NDA approval for varenicline in the U.S. (trade name “Chantix”)
September 2006	Approval in the European Union (trade name “Champix”)
May 2007	European Medicines Agency informed FDA that they were investigating a signal of suicidal-related events with varenicline and had asked Pfizer to submit a postmarketing suicidal-event analysis.
Nov 2007	Information added to ADVERSE REACTIONS section of labeling; Early communication of an ongoing safety review
Jan 2008	Serious neuropsychiatric adverse events information upgraded to the WARNINGS AND PRECAUTIONS section of the labeling
Feb 2008	Public health advisory issued
April 2008	Center Director briefing concerning varenicline and serious neuropsychiatric adverse events: discussed the benefits of varenicline to help patients achieve smoking cessation vs. the risk of serious neuropsychiatric adverse events
May 2008	Added MedGuide-only REMS; issued a postmarketing required study/clinical trial; Updated public health advisory; FAA bans use of varenicline by pilots and air traffic controllers
July 2009	Added BOXED WARNING section to varenicline and bupropion labeling; Public health advisory issued regarding addition of boxed warning to both varenicline and bupropion
Oct 2011	Drug Safety Communication issued reporting the results of two FDA-sponsored epidemiology studies that evaluated the risk of serious neuropsychiatric adverse events associated with varenicline

### ***AERS Reviews- 2008***

Prior to the addition of the boxed warning for serious neuropsychiatric adverse events, the Division of Adverse Event Analysis II<sup>1</sup> completed two reviews of AERS<sup>2</sup> cases- one

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<sup>1</sup> The Division of Adverse Event Analysis II is now called the “Division of Pharmacovigilance II”.

<sup>2</sup> The FDA Adverse Events Reporting System was called “Adverse Event Reporting System (AERS)” at the time these reviews were done.

focused on suicidality events (finalized July 2008) and the other focused on neuropsychiatric adverse events not related to suicidality (finalized Dec 2008).

Briefly, the review of suicidality events showed that from initial marketing through November 2007, AERS had 262 cases of suicidal-related events for the smoking cessation drugs (varenicline, n=153; bupropion<sup>3</sup>, n=75; transdermal nicotine, n=34). Varenicline had a higher proportion of cases for suicidal ideation (76%) vs. bupropion (61%) or nicotine (47%) and a lower proportion of suicide (attempt and completed) or other self-injurious behavior (24%) than the other drugs (bupropion 39%; transdermal nicotine 53%). Median time to event was 8-14 days.

Varenicline had the largest proportion of reports (24%) in which it was explicitly stated that the suicidal event(s) were a first-time significant behavior change from the past, followed by bupropion (15%) and nicotine (none). Varenicline cases had the most reports that described pre-existing disease worsening (17%) compared to nicotine (12%) and bupropion (8%); depression was the most common pre-existing psychiatric condition that worsened for all three drugs. The overall conclusion was that AERS data suggested a possible association between suicidal events and the use of varenicline and bupropion, given that there were postmarketing cases of positive dechallenge and a few positive rechallenges, a close temporal relationship between the event and drug use, and the occurrence of suicidal events in patients without any psychiatric history.

A recommendation was made to add a BOXED WARNING section to highlight the risk of serious neuropsychiatric adverse events and to request a PMR to determine the incidence of serious neuropsychiatric adverse events with varenicline, especially in patients with preexisting psychiatric disorders. For Zyban (bupropion), which was included as a comparator in this review, there was a similar recommendation to add language to the already existing BOXED WARNING section about the risk of suicidality in those using bupropion for smoking cessation.

A review of AERS cases describing neuropsychiatric adverse events other than suicidality was completed in December 2008. Because of the increased awareness that there was “stimulated” reporting<sup>4</sup> starting in September 2007, this review was conducted from market approval through August 2007. Additionally, because there were few evaluable cases reported with nicotine replacement therapies (NRT) the review focused on only case reports for varenicline and bupropion.

For both varenicline and bupropion, anxiety and depression were the two most commonly reported events. For both drugs, ~20% of the cases reported psychosis/mania or aggression-events. For varenicline, the most common event for the psychosis/mania and aggression groups was *hallucination* and *aggression* respectively; for bupropion it was

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<sup>3</sup> Bupropion was approved for the treatment of depression as Wellbutrin about a decade before it was approved as Zyban for smoking cessation. In order to limit the review to those exposed to bupropion for the treatment of smoking cessation, included cases had to either reference bupropion by the trade name Zyban, or mention the indication of smoking cessation in the report.

<sup>4</sup> Stimulated reporting is an increase in adverse event reporting that often occurs following any risk communication or media attention to a particular safety issue due to enhanced awareness.



*paranoia* and *hostility* respectively. There was a temporal association between the two drugs and all groups of events with a median onset time between three and seven days. Positive dechallenge was reported in 33% and 63% of the varenicline and bupropion cases respectively.

For all event groups, patients with no reported psychiatric history ranged from 17 to 33% for varenicline and 13 to 30% for bupropion. For all event groups, patients with no reported concomitant psychiatric medications ranged from 4 % to 13% for varenicline and 0 to 25% for bupropion. There were more cases with varenicline (29-33%) that reported a behavioral change from the patient's past (i.e., either new experience or disease worsening) than with bupropion (0-9%).

More varenicline patients (27%-53%) had a history of psychiatric disease than bupropion (0%-20%); however, there was a portion of the bupropion population for which unknown medical history was very high (78%). The most commonly reported psychiatric history across the case series was depression and bipolar disorder. Psychiatric medication use ranged from 13% to 73% for varenicline and 21% to 70% for bupropion.

The recommendations included enhancements to the proposed BOXED WARNING section and other parts of labeling to warn of the risk of these other neuropsychiatric adverse events.

Dr. Celia Winchell, Medical Team Leader for Addiction Products, stated in her memo to the file dated 12/12/08, the following rationale for a BOXED WARNING section for varenicline and bupropion, "The need for a boxed warning was discussed extensively at the highest levels of Center management and it was determined that the events met criteria for placement in a boxed warning. Specifically, the events are of a serious nature and have adverse consequences that can be prevented by close monitoring."

### ***Risk Evaluation and Mitigation Strategy (REMS)/ Postmarketing Requirement (PMR) Clinical Trial***

As the understanding of the serious neuropsychiatric adverse events with varenicline evolved, it was determined that a REMS was necessary to ensure that the benefits of varenicline outweighed the risks. The May 16, 2008, letter that required the REMS also included issuance of a postmarketing requirement (PMR) for a clinical study or trial to assess the known serious risk of neuropsychiatric adverse events, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions. The clinical study or trial was being required because it was determined that neither an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA nor the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA would be sufficient to assess the known serious risk of neuropsychiatric adverse events, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions related to the use of varenicline products. A similar REMS and PMR was required of another smoking cessation product, bupropion (Zyban).

After internal deliberation and discussion with Pfizer and GlaxoSmithKline (sponsor of bupropion), further guidance on the PMR was issued in a letter dated June 2, 2009. As seen in the description below, FDA determined that a randomized controlled clinical trial would be required to meet the PMR goals:

A large randomized, double-blind, active- and placebo-controlled trial to compare the risk of clinically significant neuropsychiatric adverse events, including but not limited to suicidality, in individuals using varenicline, bupropion, nicotine replacement therapy, or placebo as aids to smoking cessation over 12 weeks of treatment, and to determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant neuropsychiatric adverse events compared to individuals without prior history of psychiatric disorders while using varenicline as an aid to smoking cessation. The study should be sufficiently powered to adequately assess clinically significant neuropsychiatric adverse events with each treatment and in both of the two subgroups (i.e., with and without psychiatric disorders).

After a series of discussions internally and with the sponsors, the PMR protocol was found acceptable around July 2010 (see Attachment 1 for the protocol). In recognition of the variable and ill-defined nature of the neuropsychiatric adverse events reported, and the difficulty of capturing such events in traditional MedDRA coding<sup>5</sup>, a composite endpoint was developed specifically for the PMR trial and instruments to solicit relevant events were included in the trial procedures. The primary safety endpoint is the occurrence of at least one treatment-emergent “severe” adverse event of anxiety, depression, feeling abnormal, or hostility or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide.

Two interim analyses were planned for the RCT, the first after half of the patients completed 20 weeks of the trial, and the second when 75% of patients completed the trial to that point. Pfizer’s description of the first interim analysis (submitted October 29, 2013) follows below:

IA1 was designed to assess data on the first 4,000 subjects (50% enrollment) randomized into the study (please refer to Section 2 of the interim analysis plan). The second interim analysis is planned for the first 6,000 subjects randomized (75% enrollment).

The IA1 database snapshot occurred on 5 August 2013 after all IA1 subjects had either completed the Week 20 visit or had discontinued from the study prior to the Week 20 visit. The Week 20 visit was the first scheduled in-clinic visit after the

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<sup>5</sup> MedDRA (Medical Dictionary for Regulatory Activities) is an international standardized lexicon of medical terms used to code adverse events. MedDRA was developed by the ICH (International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and released in 1999. MedDRA contains about 21,000 different preferred terms (PTs, e.g., nausea, hypotension) for various adverse events. These PTs are vertically grouped into 3 levels. The highest level for a PT is the System Organ Class, of which there are 26 (e.g., Cardiac disorders, Infections and infestations). [http://www.meddra.org/sites/default/files/guidance/file/intguide\\_17\\_1\\_english.pdf](http://www.meddra.org/sites/default/files/guidance/file/intguide_17_1_english.pdf)

treatment-emergent period (the basis of the primary study endpoint). Of the 4,001 randomized subjects captured in this snapshot, 3,921 also had data confirming at least one dose of study drug. The remaining subjects either did not receive study drug or had missing data for study drug dosing.

The results of this blinded, pooled 50% interim analysis were completed and provided to the unblinded statistician for the IDMC on 12 September 2013. The rate of the primary neuropsychiatric event endpoint was 3.98% (156/3,921). This exceeded the 3.5% threshold specified in the protocol.

As a result, the study will continue enrollment as planned until the results of the second planned interim analysis (IA2) become available. IA2 will be conducted 20 weeks after 6,000 (75%) of the subjects have been randomized.

Pfizer's description of the second interim analysis (submitted June 10, 2014) follows below:

IA2 was planned to include data from the first 75% (6,000) subjects randomized into the study. The IA2 database snapshot occurred on 24 April 2014 after all IA2 subjects had either completed the Week 20 visit or had discontinued from the study prior to the Week 20 visit. The Week 20 visit was the first scheduled in-clinic visit after the treatment-emergent period (the basis of the primary study endpoint). This snapshot included 6,005 subjects.

The results of this pooled 75% interim analysis were completed and provided to the Independent Data Monitoring Committee (IDMC) on 19 May 2014. In addition to their standard safety review, the IDMC reviewed actual and projected neuropsychiatric adverse event rates for each of the 4 treatment arms in both the neuropsychiatric and the non-neuropsychiatric cohorts and the total population to establish if the planned sample size of 8,000 was sufficient. Their recommendation was to continue the study to the target enrollment of 8,000 as specified in the protocol. The blinded rate of the primary neuropsychiatric adverse event endpoint in the total population was 4.5% (268/6005).

In July 2014, FDA was informed by Pfizer that the RCT completed enrollment, and that the final study report is expected to be submitted in the third quarter of 2015.

## **Regulatory Requirements and Guidance Recommendations for the BOXED WARNING Section and Other Relevant Sections of the Labeling**

A familiarity with the pertinent regulatory requirements and guidance recommendations of the prescribing information is useful for determining 1) If the meta-analyses and observational study data about the risk of serious neuropsychiatric adverse events support removal of the boxed warning in the varenicline labeling; and 2) How the risk information about serious neuropsychiatric adverse events should be communicated in the varenicline labeling.

### ***Prescribing Information***

The prescribing information is written for healthcare providers and must:<sup>6</sup>

- Contain a summary of the essential scientific information needed for the safe and effective use of the drug,
- Be informative and accurate and neither promotional in tone nor false or misleading in any particular, and
- Be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

### ***Adverse Reactions***

For the purposes of prescription drug labeling, an adverse reaction (AR) is an undesirable effect reasonably associated with the use of the drug. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.<sup>7</sup>

### ***Boxed Warning***

The BOXED WARNING section of the labeling must be the first section in the FULL PRESCRIBING INFORMATION, must be surrounded by a “box” (i.e., a single black line), and must contain “contraindications or serious warnings, particularly those that may lead to death or serious injury.”<sup>8</sup> This section must briefly explain the clinically significant adverse reaction or risk and refer to more detailed information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS sections. A boxed warning is ordinarily used to highlight for prescribers one of the following situations:<sup>9</sup>

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<sup>6</sup> See 21 CFR 201.56(a)

<sup>7</sup> See 21 CFR 201.57(c)(7)

<sup>8</sup> See 21 CFR 201.57(c)(1)

<sup>9</sup> See the [Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling](#) guidance

- There is an AR so *serious*<sup>10</sup> in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling AR) that it is essential that it be considered in assessing the risks and benefits of using a drug;
- There is a serious AR<sup>7</sup> that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation); or
- FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted [e.g., certain Elements to Assure Safe Use (ETASU) under Risk Evaluation and Mitigation Strategies (REMS)].

A boxed warning can also be used in other situations:<sup>8</sup>

- To highlight a warning that is especially important to the prescriber.
- For a drug that poses risk-benefit considerations that are unique among drugs in a drug class (e.g., when the drug is the only one in its class to have a particular clinically significant AR or risk and is indicated as a second line therapy because of that clinically significant AR or risk).

Boxed warnings are more likely to be based on observed serious AR, but there are instances when a boxed warning based on an expected AR would be appropriate. For example, an Embryofetal Toxicity boxed warning would be appropriate for a drug based on evidence in humans or animals that drugs in its pharmacologic class pose a serious risk of developmental toxicity during pregnancy, even though no AR was seen with the drug.<sup>8</sup>

### Removal of a Boxed Warning

There is no specific regulation or guidance that has established criteria to remove a Boxed Warning. However, if the criteria<sup>8</sup> for including a boxed warning are no longer met, it is reasonable to remove it.

### ***Warnings and Precautions***

The WARNINGS AND PRECAUTIONS section should describe serious or clinically significant AR that have occurred with the drug or risks that are expected to occur (e.g., based on the drug class; animal data raise substantial concern about the potential occurrence of the AR in humans). This section “must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.”<sup>11</sup> The following factors can be used in determining if AR are clinically significant:<sup>8</sup>

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<sup>10</sup> For the purposes of prescription drug labeling, a *serious AR* is an AR that results in the following outcomes: Death, life-threatening AR, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. Furthermore, AR may be considered serious if they jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed in this definition. See the [Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling](#) guidance.

<sup>11</sup> See 21 CFR 201.57(c)(6)

- The relative seriousness of the disease or condition being treated.
  - Non-serious AR caused by drugs intended to treat minor, self-limiting conditions may be considered clinically significant.
  - However, those same AR caused by drugs intended to treat serious or life-threatening conditions (e.g., malignancies) may be considered much less clinically significant and not appropriate for inclusion in this section.
- A high absolute risk or rate of AR occurrence
- An AR that may lead to a potentially serious outcome unless an action is taken (e.g., dosage reduction or discontinuation) to prevent a serious outcome
- An AR that could be prevented or managed with appropriate patient selection, monitoring, or avoidance of concomitant therapy.
- An AR that can significantly affect patient compliance particularly when non-compliance has potentially serious consequences.

Each WARNINGS AND PRECAUTIONS subsection should include a succinct description of a topic and should contain the following (if known):<sup>8,11</sup>

- A succinct description of the serious or clinically significant AR or risk
- Known risk factors for the AR
- Outcome
- Numerical estimate of the risk or AR rate
- Steps to take to prevent, mitigate, monitor, or manage the AR

### ***Contraindications***

The CONTRAINDICATIONS section must describe situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal AR) clearly outweighs any possible therapeutic benefit. These situations include the use of the drug in a subpopulation of patients that have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed.<sup>12</sup> Contraindications may be based on:<sup>8</sup>

- Observed AR
- Anticipated AR supported by data (e.g., pharmacology, chemistry, or drug class data; or animal data) and the likelihood and severity of the AR

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<sup>12</sup> See 21 CFR 201.57(c)(5)

## Usage of Smoking Cessation Prescription Products

The overall sales of various smoking cessation products from manufacturer to various distributors, for both prescription (Rx) and over-the-counter (OTC) products, decreased by about 36% from approximately 9.5 million bottles/packages sold in 2009 to 6.1 million bottles/packages sold in 2013. During 2013, prescription products accounted for approximately 52% (3.1 million bottles/packages) and OTC products accounted for approximately 48% (2.9 million bottles/packages) of the total sales of smoking cessation products.<sup>13</sup> See Attachment 2 for a full review of the patterns of smoking cessation product usage.

Among prescription smoking cessation products, varenicline accounted for the vast majority of utilization. The number of prescriptions dispensed for varenicline increased from approximately 30 prescriptions dispensed during the 2nd quarter of 2006 (approval in May 2006) to a peak of approximately 2 million prescriptions dispensed in the 4th quarter of 2007 and then eventually decreased to approximately 531,000 prescriptions dispensed in the 1st quarter of 2014.<sup>14</sup>

The number of patients receiving dispensed prescriptions for varenicline decreased from approximately 3.9 million patients in 2007 to approximately 1.2 million patients in 2013. Patients aged 45-64 years accounted for majority of the patients receiving a dispensed prescription for varenicline. Females accounted for 53-56% of patients and males accounted for 44-47% of the total patients receiving a dispensed prescription for varenicline during the time period examined. Utilization of Zyban® (brand and generic bupropion), Nicotrol® inhaler and Nicotrol® nasal spray also decreased over time.<sup>15</sup>

The overall number of packages of OTC nicotine replacement products sold to consumers through retail settings fluctuated during the time examined with approximately 1.7 million packages sold in the 4th quarter of 2013. Among the OTC nicotine replacement products, the gum formulation accounted for the highest proportion of the total retail sales followed by lozenges and patches.<sup>16</sup>

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<sup>13</sup> IMS Health, IMS National Sales Perspectives™, Data Extracted April 2014

<sup>14</sup> IMS Health, National Prescription Audit (NPATM), Data Extracted August 2014

<sup>15</sup> IMS Health, Vector One®: Total Patient Tracker, Data Extracted May and August 2014

<sup>16</sup> IMS Health, OTC International Market Tracking (OTCIMS), Data Extracted May 2014

# Update on Reporting of Neuropsychiatric Adverse Events to FAERS

The Division of Pharmacovigilance II conducted a case-level review of recently (2013-2014) submitted FAERS data for varenicline and serious neuropsychiatric adverse events, as requested by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) in support of the October 16, 2014, Advisory Committee meeting. This case-level review (Attachment 3) followed an assessment of overall trends in case reporting of serious neuropsychiatric adverse events to FAERS for the years 2008-2013 (Attachment 4). These assessments provide an update to two prior reviews completed by the Division in 2008 (Attachments 5 and 6).<sup>17,18</sup>

A total of 105 FAERS cases of varenicline and serious psychiatric events were found during the time period of 1/1/13 to 6/30/14 where a significant behavior change in association with varenicline was stated or implied. These cases consisted of suicidality, psychosis, mania, aggression or other neuropsychiatric adverse events (e.g., depression), and were consistent with the findings of the 2008 reviews, that led to the current Boxed Warning. Characteristics of the events in this review as well as the prior reviews,<sup>17,18</sup> include:

- Neuropsychiatric adverse events occurred in patients with and without a history of psychiatric disorders
- Most events occurred while patients were on varenicline; however, some followed discontinuation of varenicline
- There was a relatively short time to event onset (median time of 10 days from starting varenicline to onset of neuropsychiatric symptoms)
- Reports included cases of resolution of neuropsychiatric adverse events following varenicline discontinuation (positive dechallenge), as well as recurrence of neuropsychiatric adverse events when varenicline was restarted (positive rechallenge)

Based upon this updated review, no changes in the varenicline label for serious neuropsychiatric adverse events in the post marketing setting are recommended.

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<sup>17</sup>Pollock M, Mosholder A, Lee J, Governale L. Suicidality associated with varenicline, bupropion, and nicotine transdermal patch. 7/16/08; OSE RCM #2007-2425.

<sup>18</sup>Pollock M, Mosholder A, Ju J. Psychiatric events (including suicides) associated with varenicline and bupropion. 12/8/08; OSE RCM# 2008-1291.



## Division of Epidemiology II Summary of Observational Studies Examining the Relationship Between Varenicline and Neuropsychiatric Adverse Events

The sponsor identified five observational studies of varenicline-associated neuropsychiatric risk (four publications and one unpublished study), including three which examined the association between varenicline and risk of neuropsychiatric medical encounters (i.e., hospitalizations, emergency room visits, and outpatient visits) and two which investigated the association between varenicline and risk of suicide, non-fatal self-harm, and initiation of an antidepressant (as a proxy of incident depression). Please see the Division of Epidemiology II's (DEPI-II) review of the labeling supplement regarding neuropsychiatric adverse events associated with varenicline (Attachment 7), for a summary of each reviewed study. One of the studies (Thomas et al) was an expansion of an earlier study (Gunnell et al).<sup>19</sup>

All the reviewed observational studies were based on population-level data reflecting the real-world smoking cessation product user population. Their inclusion of patients with a history of neuropsychiatric disorders extends the generalizability of the findings, because that population was excluded in most clinical trials conducted to date. The studies also all attempted to control for confounding by employing appropriate design and analytical approaches. Please see Table 1 for a summary of main study findings of the reviewed observational studies.

Table 1 Main study findings of the observational studies on varenicline and risk for neuropsychiatric adverse events

Study	Outcome	Analyses	Varenicline (N event/ Total/IR*)	Reference group		Fully- adjusted Hazard Ratio
				NRT (N event/ total/IR*)	Bupropion (N event/ total/IR*)	
Meyer et al. 2013	NPS hospitalization (primary diagnosis) in 30 days	New users, PS-matched	16/10,814/18	14/10,814/16	-	1.14 (0.56-2.34)
Meyer et al. 2013	NPS hospitalization (any diagnosis) in 30 days	New users, PS-matched	34/10,710/39	43/10710/49	-	0.79 (0.50-1.24)
Meyer et al. 2013	NPS Outpatients visits in 30 days	New users, PS-matched	234/10710/269	327/10710/378	-	0.71 (0.60-0.84)
VA study Unpublished	NPS hospitalization (primary diagnosis) in 30 days	New users, PS-matched	16/14,131/16	21/14,131/21	-	0.76 (0.40-1.46)
VA study Unpublished	NPS hospitalization (primary diagnosis) in 30 days	Prevalent users, PS-matched	29/12,258/29	94/24,185/47	-	0.74 (0.49-1.14)

<sup>19</sup> Both Thomas et al and Gunnell et al studies were based on the same source data (CPRD) with overlapping time-frames, but Thomas et al included a longer time-frame and linked to two other data sources to enhance outcome ascertainment

Pasternak et al, 2013	NPS emergency room visit or hospitalization in 30 days	New users, PS-matched	39/17,975/27	-	46/17,935 /31	0.85 (0.55-1.30)
Gunnell et al. 2009	Suicide or non-fatal self-harm in 90 days	Prevalent users	18/10,973/5.3*	141/63,265/7.5 *	-	1.12† (0.67-1.88)
Gunnell et al. 2009	Suicide thoughts in 90 days	Prevalent users	5/10,973/NA	30/63,265/NA	-	1.43† (0.53-3.85)
Thomas et al. 2013	Suicide or non-fatal self-harm in 90 days	New users	19/30,352/3	69/78,407/4	-	0.88& (0.52-1.49)
Gunnell et al. 2009	Initiation of antidepressants in 90 days‡	Prevalent users	292/9162/NA	1792/49415/NA	-	0.88† (0.77-1.00)
Thomas et al. 2013	Initiation of antidepressants in 90 days*	New users	255/18,386/57	799/42,475/77	-	0.75& (0.65-0.87)

NRT: Nicotine replacement therapy; IR: Incidence Rate=event/1,000 person-year; NPS: neurologic/psychiatric; PS: propensity score

Hazard Ratios calculated using Cox proportional hazards regression model

\*age and sex-standardized

†Adjusted for age; sex; use of hypnotics, antipsychotics, and antidepressants; alcohol misuse; previous suicide related event; previous smoking cessation therapy; psychiatric consultation; date of initial exposure to product, number of general practice visits per year, index of multiple deprivation, UK region.

&Adjusted for sex; age; previous psychiatric illness or consultation; previous use of psychotropic drugs such as hypnotics, antipsychotics and antidepressants; previous self-harm; socioeconomic position; major chronic illness; number of general practice consultations in the year before the prescription; exposure to the drug before or after 2008; year of first prescription; and previous use of a smoking cessation product.

‡Restricted to those with no antidepressants in the six months before smoking cessation therapy.

\*Restricted to those with no previous antidepressant use

As depicted in Table 1, the 95% confidence interval of the outcome risk estimates mostly included 1.0. The only findings that achieved statistical significance are the reduced risk of outpatient neuropsychiatric visits (the VA study) and the reduced risk of initiation of antidepressant therapy (the Thomas et al. study) associated with varenicline (Table 1). However, these two outcome measures are not specific in measuring treatment emergent neuropsychiatric adverse events related to varenicline. Outpatient neuropsychiatric visits may be simply capturing pre-existing psychiatric comorbidities, rather than treatment emergent psychiatric events. Because antidepressants are also used to treat multiple other disorders, including non-psychiatric indications, prescribing of antidepressants cannot be viewed as a specific measure of incident depression.

Although none of the reviewed studies observed a significant increase in the risk of serious neuropsychiatric adverse events (i.e., neuropsychiatric hospitalization or emergency room visit, fatal or non-fatal self-harm) between varenicline and the comparator (bupropion or nicotine replacement therapy), they do not provide reassuring evidence of the absence of risk. Please see DEPI-II's review, for details of the specific limitations of these studies.

Briefly, the following study limitations have been identified:

- the incompleteness of ascertainment of the examined outcomes;

- the lack of validation of the diagnostic codes used to identify the examined outcomes;
- the use of bupropion (another smoking cessation drug with neuropsychiatric risk) as a comparator;
- the likely presence of “channeling bias” (sicker patients being channeled away from treatment with varenicline);
- the likely presence of residual confounding between varenicline users and nicotine replacement therapy (NRT) users; and
- the limited statistical power.

The observational studies reviewed provided evidence of insufficient quality to either rule in or rule out an increased risk of suicide, non-fatal self-harm, or neuropsychiatric hospitalizations associated with varenicline use. The available observational data also cannot be used to “cap” the varenicline-associated risk for neuropsychiatric outcomes due to the high probability of under-ascertainment of these outcomes in the existing studies. Therefore, the true upper limit of the 95% confidence interval for varenicline-associated neuropsychiatric risk is unknown based on these data. It is our hope that the required post-marketing clinical trial that the sponsor is conducting may allow for more complete risk ascertainment, even though the generalizability of the findings may be limited.

## Division of Biostatistics VII Summary of Meta-analyses

A meta-analysis was conducted to evaluate the risk of psychiatric events associated with varenicline relative to placebo in two sets of trials:

- A set of 5 Phase III/IV clinical trials that captured the risk of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS). This set of trials is referred to as the “5-Study Cohort”. It consisted of 1907 randomized subjects: 1130 subjects randomized to varenicline and 777 subjects randomized to placebo.
- A set of 18 Phase II-IV clinical trials, including the trials in the 5-Study Cohort, which captured psychiatric adverse events through MedDRA codes. This set of trials is referred to as the “18-Study Cohort”. It consisted of 8521 randomized subjects: 5072 subjects randomized to varenicline and 3449 subjects randomized to placebo.

To characterize the risk of psychiatric events several endpoints of interest were analyzed.

- Percent of subjects responding “yes” for suicidal ideation (any type) and/or suicidal behavior (any type) based on the C-SSRS.
- Percent of subjects who experienced an Adverse Event (AE) in the Suicide/Self-injury MedDRA Standardized MedDRA Query (SMQ).
- Percent of subjects who experienced an adverse event in the Hostility/Aggression MedDRA SMQ.
- Percent of subjects who experienced an adverse event in the MedDRA Psychiatric disorders system organ class (SOC).
- Percent of subjects experiencing an event in the composite endpoint<sup>20</sup> specified in ongoing trial A3051123 intended to fulfill the PMR issued in 2008 (PMR endpoint).

Table 2 summarizes the meta-analysis of psychiatric adverse events observed while patients were on randomized treatment or within a window of 30 days after treatment discontinuation. This meta-analysis showed no evidence of increased risk of psychiatric adverse events associated with varenicline relative to placebo.

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<sup>20</sup> PMR endpoint is defined as “at least one treatment emergent “severe” adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide.”

**Table 2. Summary of Meta-Analysis of Treatment Emergent Endpoints**

<b>Endpoint</b>	<b>No. Trials</b>	<b>Total events</b>	<b>RR (95% CI)</b>
Suicidal Ideation or Behavior	5	55	0.79 (0.46, 1.36)
Suicide / Self-Injury SMQ	18	25	0.45 (0.19, 1.07)
Hostility / Aggression SMQ	18	46	1.10 (0.60, 2.03)
Psychiatric Disorders SOC	18	981	1.03 (0.84, 1.25)
PMR endpoint	18	245	0.85 (0.64, 1.13)

The meta-analysis has the following limitations:

- All analyses in the 18-Study Cohort were conducted retrospectively. Adverse events of interest were not collected prospectively and, therefore, it is possible that some adverse events may have been underreported in these trials. Specifically, as shown in Section 4.2 of the attached statistical background document, the suicide/self-injury SMQ did not capture some suicide-related adverse events when compared to the C-SSRS instrument. It is possible that the other SMQs in the meta-analysis may have also failed to capture some psychiatric adverse events.
- Forty-eight out of the 55 events in the analysis of suicidal ideation and behavior based on the C-SSRS instrument were observed in two trials that enrolled patients with history of schizophrenia or depression. Only seven events were observed in the other three trials that collected the C-SSRS.
- MedDRA SMQs and SOCs may include adverse events of different severities. It is possible that the SMQs in this meta-analysis may not be adequate to characterize the risk of rare but severe adverse events.

See Attachment 8 for the detailed statistical review.

## Discussion/ Interim actions

The original signal for serious neuropsychiatric adverse events came from cases reported to the FDA and described in the medical literature. In this supplement, Pfizer argues that the information garnered from the meta-analyses they conducted and the published observational studies they have reviewed is reassuring and trumps the information culled from the case reports that originally led to the Boxed Warning and Warnings and Precautions statements in varenicline labeling, and that the sum of this new evidence no longer supports the need for a boxed warning for serious neuropsychiatric adverse events.

As summarized above, DB VII and DEPI-II have concerns about the validity of the findings from Pfizer's meta-analyses and the published observational studies. The limitations of the findings described in each of their reviews and summarized in this document raise questions as to how to best interpret the findings of the meta-analyses and observational studies.

Furthermore, when FDA issued the postmarketing requirement for the randomized controlled trial to evaluate the neuropsychiatric adverse events with varenicline, FDA stated that observational studies would not be adequate to address this safety question. This decision was made because there was a lack of confidence that the kinds of coded data used in observational studies could capture the neuropsychiatric adverse events of interest, and concern about differential selection of patients for treatment with varenicline and the associated bias that could be introduced into comparisons. The required clinical trial includes randomization to treatment, and the neuropsychiatric outcome of interest was custom-crafted as a composite outcome of a series of neuropsychiatric adverse events of a certain severity to specifically capture the kinds of events described in the spontaneous reports.

Based on FDA's review of the meta-analyses and observational studies submitted by Pfizer, FDA has determined that some information about these data could be included in the varenicline labeling (Attachment 10, Section 5.1) so that prescribers have a full picture of what analyses and studies have been conducted to enhance the understanding of varenicline-associated serious neuropsychiatric adverse events.

However, the determination of whether to remove a boxed warning is a decision for which there is limited precedent. FDA believes that the randomized controlled trial prospectively designed to evaluate the risk of serious neuropsychiatric adverse events with varenicline, whose final study report is expected in a year, should be reviewed and considered as part of such a regulatory action. However, because Pfizer believes the collection of observational and meta-analytic data are alone sufficient, we are bringing this issue to the Committee for discussion.



**A PHASE 4, RANDOMIZED, DOUBLE-BLIND, ACTIVE AND PLACEBO  
-CONTROLLED, MULTICENTER STUDY EVALUATING THE  
NEUROPSYCHIATRIC SAFETY AND EFFICACY OF 12 WEEKS VARENICLINE  
TARTRATE 1 MG BID AND BUPROPION HYDROCHLORIDE 150 MG BID FOR  
SMOKING CESSATION IN SUBJECTS WITH AND WITHOUT A HISTORY OF  
PSYCHIATRIC DISORDERS**

<b>Compound:</b>	CP-526,555
<b>Compound Name (if applicable):</b>	Varenicline Tartrate
<b>US IND Number (if applicable):</b>	58,994
<b>EudraCT Number:</b>	2010-022914-15
<b>Protocol Number:</b>	A3051123
<b>Phase:</b>	Phase 4
	Amendment 7, 07 November 2012

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APPROVED BY PFIZER FOR PUBLIC DISCLOSURE

### Document History

Document	Version Date	Summary of Changes
Amendment 7	07 November 2012	<p>This is being amended to incorporate changes based on the updated bupropion Global Data Sheet dated 18 Sep 2012.</p> <ul style="list-style-type: none"> <li>Sections 6.2.2 Clinic Visits (Week 1 to 6 Visits, Weeks, 8, 10, 12 and ET<sub>12</sub>) and 6.3.1 Clinic Visits (Weeks 13, 16, 20, 24 and ET<sub>24</sub> Visit): Added pregnancy testing to Visit Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16.</li> </ul> <p>Section 6.4.1 Subject Withdrawal is updated to include:</p> <ul style="list-style-type: none"> <li>Study drug will be discontinued immediately for any female subject who becomes pregnant during the treatment period of the study.</li> </ul> <p>Section 7.1.14 Laboratory was updated to include the additional pregnancy testing at clinic visits</p> <p>Section 8.9 Exposure During Pregnancy was updated to match the most recent protocol template and Pfizer SOPs</p>
Amendment 6*	30 May 2012  <b>Country Specific:</b> Bulgaria, Denmark, Finland, France, Germany, Slovakia and Spain	<p>This is being amended to incorporate changes based on feedback from the FDA and regulatory agencies in the EU.</p> <ul style="list-style-type: none"> <li>Vital signs (PR and BP) are added to all clinic visits.</li> <li>ECG is added to Week 12 and ET12 visit.</li> <li>Section 4.2 Exclusion Criteria #9 is being changed from Subjects with a seizure disorder to Subjects with a current seizure disorder or any history of seizures. This change is to be consistent with EU SMPC for bupropion</li> <li>Section 4.2 Exclusion Criteria #23 is added to exclude subjects with skin conditions which would hinder the use of NRT placement.</li> <li>Section 6. (Study Procedures) is updated to include additional vital signs at every clinic visit and ECG at Wk 12 or ET12.</li> <li>Section 6.4. (Subject Withdrawal) is updated to include information for Off Treatment in Study (OTIS) subjects and all subjects will be followed until final visit unless they withdraw consent.</li> <li>Section 7.1.14. (Physical Examination, Vital Signs and Electrocardiogram) is updated to include vital signs at every clinic visit and ECG as Wk 12 or ET12.</li> <li>Section 7.1.15 (Cardiovascular Events of Interest) is changed from: Hospitalization for angina pectoris or chest pain to: Hospitalization for unstable angina. Also wording was added to further clarify how events of interest will be identified, reviewed and adjudicated.</li> </ul> <p>In addition the following changes/updates are made:</p> <ul style="list-style-type: none"> <li>Remove Czech Republic from header and title page as this protocol is no longer being submitted to this country.</li> </ul>

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		<ul style="list-style-type: none"> <li>Section 4.2. Exclusion Criteria #5 is updated to clarify intent. It was changed from: “Subjects with a positive urine drug screen at screening or baseline”. To: Subjects with a positive urine drug screen at screening or baseline for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition.</li> <li>Section 5.3.3. Study Drug Administration- additional instructions for clarity are added to perform dose reduction of study drugs and if drug needs to be permanently discontinued. Section also updated to add information on medication error reporting.</li> <li>Section 5.5. Concomitant Medication: Milnacipran (Scavella) is added to any use prohibited.</li> <li>Section 7.1.10 Typographical error is corrected.</li> <li>Section 8 Updated various Adverse Event sections to match the most recent protocol template and Pfizer SOPs.</li> <li>Section 15 Publication of Study Results updated to match the most recent protocol template and Pfizer SOPs.</li> </ul>
Amendment 5	30 May 2012	<p>This is being amended to incorporate changes based on feedback from the US FDA and regulatory agencies in the EU.</p> <ul style="list-style-type: none"> <li>Vital signs (PR and BP) are added to all clinic visits.</li> <li>ECG is added to Week 12 and ET12 visit.</li> <li>Section 4.2 Exclusion Criteria #22 is added to exclude subjects with skin conditions which would hinder the use of NRT placement.</li> <li>Section 6 (Study Procedures) is updated to include additional vital signs at every clinic visit and ECG at Wk 12 or ET12.</li> <li>Section 6.4 (Subject Withdrawal) is updated to include information for Off Treatment in Study (OTIS) subjects and all subjects will be followed until final visit unless they withdraw consent.</li> <li>Section 7.1.12 (Physical Examination, Vital Signs and Electrocardiogram) is updated to include vital signs at every clinic visit and ECG as Wk 12 or ET12</li> <li>Section 7.1.15 (Cardiovascular Events of Interest) is changed from: Hospitalization for angina pectoris or chest pain to: Hospitalization for unstable angina. Also wording was added to further clarify how events of interest will be identified, reviewed and adjudicated.</li> </ul> <p>In addition the following changes/updates are made:</p> <ul style="list-style-type: none"> <li>Section 4.2 Exclusion Criteria #5 is updated to clarify intent. It was changed from: “Subjects with a positive urine drug screen at screening or baseline”. To: Subjects with a positive urine drug screen at screening or baseline for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition</li> <li>Section 5.3.3 Study Drug Administration- additional instructions for clarity are added to perform dose reduction of study drugs and if drug needs to be permanently discontinued. Section also updated to add information on medication error reporting.</li> <li>Section 5.5 Concomitant Medication: Milnacipran (Scavella) is added to any use prohibited.</li> </ul>

		<ul style="list-style-type: none"> <li>Section 7.1.10 Typographical error is corrected.</li> <li>Section 8 Updated various Adverse Event sections to match the most recent protocol template and Pfizer SOPs.</li> <li>Section 15 Publication of Study Results updated to match the most recent protocol template and Pfizer SOPs.</li> </ul>
Amendment 4*	10 October 2011  Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Slovakia and Spain.	This protocol is being amended to incorporate changes requested by the EMA. <ul style="list-style-type: none"> <li>Subjects with Bipolar I and II disorders will be excluded from the study.</li> </ul> The Mental Health Professional (MHP) will be defined as a psychiatrist only.
Amendment 3	04 Oct 2011	This protocol is being amended to incorporate changes requested by the US FDA. The protocol is being amended to include detailed cardiovascular medical history, collection of cardiovascular events of interest during the study, and a Cardiovascular Event Adjudication Committee. The protocol was also updated to be consistent with updated SOP CT 02 in regards to Section 15.1, Communication of Results by Pfizer.
Amendment 2	28 June 2011	The protocol is being amended to incorporate changes requested by the US FDA and the EMA. In addition, bupropion has been added to the title, objectives and endpoints as an active comparator. The amendment also incorporates changes to the <a href="#">Neuropsychiatric Adverse Events Interview (NAEI)</a> based on the outcome of the pilot in a similar patient population. In addition, the amendment provides updates to be in compliance with Pfizer SOPs, clarifies certain protocol aspects and corrects inconsistencies/ typographical errors. <ul style="list-style-type: none"> <li>Updates safety and efficacy endpoints to include bupropion as active comparator;</li> <li>Defines current and past diagnosis of a psychiatric history for the <a href="#">Inclusion Criteria</a>;</li> <li>Clarification of the exclusion criteria for which bupropion is not appropriate;</li> <li>Clarification of the randomization criteria within the cohort for a psychiatric disorder;</li> <li>Additional information of re-screening of subjects;</li> <li>Additional verbiage for subjects lost to follow up during the study;</li> <li>Clarification of the <a href="#">Clinical Global Impression of Improvement (CGI-I)</a> and how to rate the severity for those subjects with a psychiatric history;</li> </ul>

		<ul style="list-style-type: none"> <li>• Clarification of when the lack of efficacy should be reported as an adverse event;</li> <li>• Updates to the statistical sections to include bupropion in the analyses;</li> <li>• Changes to the <a href="#">Nicotine Use Inventory (NUI)</a> to comply with US FDA requests and ensure proper data collection</li> <li>• Changes to the NAEI based on the outcome of the NAEI pilot study.</li> <li>• Updates to include language on potential cases of drug induced liver injury.</li> <li>• Updates <a href="#">Appendix 9</a>, and <a href="#">Appendix 10</a> (C-SSRS Baseline and Since Last Visit) to January 14, 2009 version).</li> </ul>
Amendment 1	17 June 2010	See <a href="#">Appendix 13</a>
Original protocol	17 May 2010	N/A

For Amendments: This amendment incorporates all revisions to date except those in the amendment(s) indicated with an (\*). The sites following the amendment(s) marked with an (\*) above must use the specific region/country/site amendments as well as the current amendment.

## SCHEDULE OF ACTIVITIES- Study Treatment Period

Procedure	Screen	BL	Wk 1 (Day 8)	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7*	Wk 8	Wk 9*	Wk 10	Wk 11*	Wk 12	ET <sup>a</sup> 12
Informed Consent <sup>b</sup>	X														
Medical History, Cardiovascular Medical History, Demography, Smoking history/ height	X														
Physical Examination	X														
Vital Signs (PR, BP)		X	X	X	X	X	X	X		X		X		X	X
Weight		X												X	X
SCID I and II	X														
Adverse Events Volunteered reporting		X	X	X	X	X	X	X		X		X		X	X
Concomitant Medications and Non-Drug Treatment	X	X	X	X	X	X	X	X		X		X		X	X
CGI-S	X	X													
CGI-I			X	X	X	X	X	X		X		X		X	X
HADS		X	X	X	X	X	X	X		X		X		X	X
Aggression Questionnaire		X													
Neuropsychiatric Adverse Event Interview (NAEI)		X	X	X	X	X	X	X		X		X		X	X
SBQ-R	X														
C-SSRS	X	X	X	X	X	X	X	X		X		X		X	X
NUI		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fagerström Test	X														
Exhaled CO	X	X	X	X	X	X	X	X		X		X		X	X
Dispense Study Drugs		X	X	X	X	X	X	X		X		X			
EKG	X													X	X
CBC, Blood Chemistry	X													X	X
Pregnancy Test <sup>c</sup> (urine or serum)	X	X	X	X	X	X	X	X		X		X		X	X
Urine Drug Screen <sup>d</sup> (dipstick at site)	X	X													
Emergency Contact Information Card		X													
Counseling (≤10 minutes)		X	X	X	X	X	X	X		X		X		X	X
Psychiatric Evaluation <sup>e</sup>	X	X	X	X	X	X	X	X		X		X		X	X
Collect cardiovascular events of interest			X	X	X	X	X	X	X	X	X	X	X	X	X

\* Designates telephone visit

<sup>a</sup> If ET is before the Week 12 visit.

<sup>b</sup> Must be signed prior to any protocol procedures being performed.

<sup>c</sup> All females unless surgically sterilized or at least 2 years postmenopausal.

<sup>d</sup> May be performed at other visits at investigator's discretion.

<sup>e</sup> If deemed needed per protocol section 7.1.10.

## SCHEDULE OF ACTIVITIES- Post - Treatment Period

Procedure	Wk 13	Wk 14*	Wk 15*	Wk 16	Wk 17*	Wk 18*	Wk 19*	Wk 20	Wk 21*	Wk 22*	Wk 23*	Wk 24	ET <sup>a</sup> 24
Vital Signs (PR, BP)	X			X				X				X	X
Weight												X	X
Adverse Events Volunteered reporting	X			X				X				X	X
CGI-I	X			X				X				X	X
HADS	X			X				X				X	X
Neuropsychiatric Adverse Event Interview	X			X				X				X	X
C-SSRS	X			X				X				X	X
NUI	X	X	X	X	X	X	X	X	X	X	X	X	X
Exhaled CO	X			X				X				X	X
Concomitant Medications and Non-Drug Treatment	X			X				X				X	X
Counseling (≤10 minutes)	X			X				X				X	X
Psychiatric Evaluation <sup>b</sup>	X			X				X				X	X
Collect cardiovascular events of interest	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test <sup>c</sup> (urine or serum)				X									

\* Designates telephone visit.

<sup>a</sup> If ET is after Week 12 visit and before Week 24 visit.

<sup>b</sup> If deemed needed per protocol section 7.1.10.

<sup>c</sup> All females unless surgically sterilized or at least 2 years postmenopausal.

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## 1. INTRODUCTION

### 1.1. Indication

Aid to smoking cessation treatment.

### 1.2. Background and Rationale

#### Varenicline

Varenicline was approved as Chantix<sup>®</sup> by the US FDA in May 2006, and as Champix<sup>®</sup> by the EMEA in September 2006, and is now approved in more than 90 countries worldwide for smoking cessation in adults. The approved dose regimen is 1-mg twice daily (1 mg BID) for 12 weeks starting with a 1-week titration.

Protocol A3051123 is a Phase 4 study being conducted to assess varenicline as an aid to smoking cessation treatment in subjects with and without an established diagnosis of major psychiatric disorder and to characterize the neuropsychiatric safety profile in both of these cohorts. This study qualifies as a Post-Authorization Safety Study (PASS) and it is a US Post-Marketing Requirement and an EU Post-Approval Commitment. The population will be characterized by presence or absence of an established and stable diagnosis of major psychiatric disorder, current or past, Diagnostic and Statistic Manual of Mental Disorders 4<sup>th</sup> Edition Text Revision DSM IV TR-defined. This is described as “diagnosis of psychiatric disorder” throughout the protocol.

Literature has shown that subjects with a current Axis I disorder were more likely to experience tobacco withdrawal symptoms and withdrawal-related discomfort and relapse. Subjects with Axis I disorders may need more intensive and/or longer treatments to help them cope with withdrawal symptoms and prevent relapse.<sup>11</sup>

In Phase 3, subjects with psychiatric disorders were not included per protocol by the use of the following exclusion criteria; “Subjects currently or within the past 12 months requiring treatment for depression. Subjects with current or prior history of panic disorder, psychosis, or bipolar disorder”. In this study, recruitment will be balanced equally with respect to subjects with and without a diagnosis of major psychiatric disorder to allow for the assessment of neuropsychiatric events in each of the cohorts and each of the treatment groups. Subjects will be randomized to receive varenicline, placebo, bupropion hydrochloride or transdermal nicotine patch (NRT), the latter two being included as active controls.

Varenicline is a selective nicotinic acetylcholine receptor (nAChR) partial agonist designed to have specific and potent binding at the  $\alpha 4\beta 2$  receptor subtype, which mediates the reinforcing effects of nicotine. Because of its mixed agonist-antagonist properties, varenicline offers the therapeutic benefit of relieving symptoms of nicotine withdrawal and cigarette craving during abstinence while blocking the reinforcing effects of chronic nicotine. Because of its high selectivity for  $\alpha 4\beta 2$  nicotinic receptors, at therapeutic levels,<sup>3</sup> varenicline does not bind to other neurotransmitter receptors and transporters,<sup>9</sup> including those implicated in mental disorders.<sup>2</sup>

Phase 2 to Phase 4 placebo controlled clinical trials have demonstrated the efficacy and tolerability of varenicline 1 mg BID in more than 3000 cigarette smokers, increasing the odds of quitting approximately 4-fold compared with placebo at end of treatment, and nearly 2-fold compared with bupropion at end of treatment. The most frequently reported treatment-emergent adverse events associated with varenicline were nausea, sleep disturbance, constipation, flatulence and vomiting. Nausea was reported by approximately 30% of patients treated with varenicline 1 mg BID after an initial week of dose titration compared with 10% in patients taking placebo. In patients taking 0.5 mg BID following initial titration, the incidence was 16% compared with 11% for placebo. Nausea was generally described as mild or moderate and often transient.

### Post Marketing Experience

There have been post-marketing reports of neuropsychiatric symptoms, some serious, including changes in mood, agitation, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, changes in behavior, anxiety, panic, suicidal ideation, suicide attempt and completed suicide in patients attempting to quit smoking with varenicline. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish causal relationship to drug exposure or smoking status. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. The role of varenicline in these reports is not known. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness.

There have also been reports of serious skin reactions and hypersensitivity reactions, including angioedema.

### Bupropion

Bupropion was first approved for the treatment of depression (as Wellbutrin™) on 30 December 1985 in the USA. The first approval for smoking cessation (as Zyban™) was in 1996, also in the USA. Bupropion has been approved for depression in approximately 70 countries worldwide and for smoking cessation in almost 90 countries. Post-marketing exposure is estimated to be 90 million patient exposures for all bupropion formulations and indications, of which approximately 24 million are for use in smoking cessation.

Zyban™ was the first non-nicotine treatment for nicotine dependence as an aid to smoking cessation. Zyban™ is chemically unrelated to nicotine or other agents currently used in the treatment of nicotine addiction. Bupropion is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin) and does not inhibit monoamine oxidase. The mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms. Bupropion increases dopamine concentrations in the nucleus accumbens in rats. While the clinical significance is unknown, this action may mimic the effects of nicotine and reduce cravings associated with nicotine addiction. Bupropion also reduces noradrenergic neuron

firing in the locus ceruleus of rats. While this may explain the reduction in nicotine withdrawal symptoms, the clinical significance is unknown. In clinical trials, treatment with bupropion reduced withdrawal symptoms compared to placebo and also showed evidence of reduction in craving for cigarettes or urge to smoke compared to placebo.

The efficacy of bupropion for the treatment of nicotine dependence as an aid to smoking cessation was evaluated in clinical studies of 1,508 non-depressed, chronic cigarette smokers. Two randomized, placebo-controlled trials were conducted:

- A dose-response trial of Zyban™ 100 mg/day (50 mg BID), 150 mg/day, 300 mg/day (150 mg BID), and placebo;
- A comparative trial of Zyban™, Habitrol® (nicotine transdermal system – NTS; also marketed as Nicotinell® by Novartis in some countries), the combination of Zyban™ and NTS, and placebo.

In both clinical trials, patients treated with Zyban™ achieved a higher four-week continuous quit rate than placebo-treated patients. In addition, Zyban™ was more effective than NTS in the comparative study. The combination of Zyban™ and NTS produced the highest rates of continuous abstinence, although not statistically significantly different from Zyban™ alone. In the dose-response trial, patients treated with Zyban™ 300 mg/day (150 mg BID) maintained a significantly higher abstinence rate than those treated with placebo through the end of six months.

Zyban™ was generally well tolerated by chronic cigarette smokers enrolled in the clinical trials. The most common adverse events consistently observed with Zyban™ were dry mouth and insomnia. Both of these events may be dose related. Bupropion is likely to have a low potential for abuse, and there was no evidence of withdrawal phenomena upon abrupt cessation of Zyban™.

Placebo-controlled Phase 3 and Phase 4 studies of bupropion for smoking cessation generally excluded patients who had a psychiatric disorder (eg, major depressive episode, bipolar disorder, panic disorder, psychosis) or who were taking psychoactive drugs. This study qualifies as a Post-Authorization Safety Study (PASS) and it is a US Post-Marketing Requirement.

#### Post Marketing Experience

Seizure is the most medically-significant dose-related adverse reaction associated with bupropion. A postmarketing surveillance study and pooling of clinical trial data have shown the incidence for the sustained-release tablet to be approximately 0.1% in therapeutic doses. Hypersensitivity reactions are also important adverse events that occur with bupropion.

Neuropsychiatric symptoms have been reported. In particular, psychotic and manic symptomatology has been observed, mainly in patients with a known history of psychiatric illness. The following neuropsychiatric reactions are listed in the Adverse Reactions section of the bupropion Core Data Sheet (CDS), the frequency of which have been estimated from

integrated placebo-controlled smoking cessation studies or postmarketing reports: insomnia, depression, confusion, delusions, paranoid ideation, hallucinations, agitation, restlessness, anxiety, irritability, hostility, aggression, depersonalisation, abnormal dreams, concentration disturbance and dizziness.

Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in patients undergoing a smoking cessation attempt. These symptoms have also been reported during bupropion treatment, and generally occurred during the early stages of treatment.

Bupropion is indicated for the treatment of depression in some countries. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adults with major depressive disorder and other psychiatric disorders showed an increased risk of suicidal thinking and behavior associated with antidepressant use compared to placebo in patients less than 25 years old.

Clinicians should be aware of the possible emergence of significant depressive symptoms or suicidal ideation in patients being treated with bupropion, and should advise and monitor patients accordingly.

### **Single Reference Safety Document**

The Single Reference Safety Document for varenicline is the Core Data Sheet. The Single Reference Safety Documents for Bupropion and NRT are the respective Core Data Sheets (CDS).

## **2. STUDY OBJECTIVES AND ENDPOINTS**

### **2.1. Objectives**

#### **2.1.1. Safety**

##### **Primary Safety Objectives:**

1. To characterize the neuropsychiatric safety profiles of varenicline and bupropion by estimating the differences from placebo in the incidence of the primary neuropsychiatric AE endpoint for subjects:
  - a. With a diagnosis of psychiatric disorder;
  - b. Without a diagnosis of psychiatric disorder.
2. To characterize the differences in the neuropsychiatric safety profiles of varenicline and bupropion as compared with placebo between these sub-populations (cohorts).

### **2.1.2. Efficacy: Abstinence from Smoking**

Main Efficacy Objective: To compare smoking abstinence rates of varenicline and bupropion relative to placebo for the last 4 weeks of treatment and continuously through Week 24, as measured by CO-confirmed continuous abstinence rate (CAR) CAR9-12 and CAR9-24, respectively, separately for subjects with and without a diagnosis of psychiatric disorder.

#### **Secondary Objective:**

To assess if there is a difference between cohorts in the placebo adjusted relative abstinence rates (CAR9 12 and CAR9 24) of varenicline and bupropion, separately.

Another secondary objective of the study is to perform the following comparisons with respect to the primary safety and efficacy endpoints:

1. NRT vs. Placebo;
2. Varenicline vs. Bupropion;
3. Varenicline vs. NRT;
4. Bupropion vs NRT.

## **2.2. Endpoints**

### **2.2.1. Safety**

The primary safety endpoint is the occurrence of at least one treatment emergent “severe” adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. This endpoint is referred to as the Neuropsychiatric (NPS) AE endpoint.

#### **Secondary Safety Endpoints:**

- Occurrence of the components of the primary safety endpoint;
- Individual item responses, along with subscale scores and overall score (when applicable; specifics are stated in the Statistical Analysis Plan), for the following questionnaires:
  - Hospital Anxiety and Depression Scale (HADS) [Appendix 2](#);
  - Columbia Suicide Severity Rating Scale (C-SSRS) [Appendix 10](#);
  - Clinical Global Impression of Improvement (CGI-I) [Appendix 8](#).

### **2.2.2. Efficacy**

The main efficacy endpoint is 4-week CO-confirmed continuous abstinence for Weeks 9 through 12.

#### **Secondary Efficacy Endpoints:**

The secondary efficacy endpoint is CO-confirmed continuous abstinence from Week 9 through Week 24.

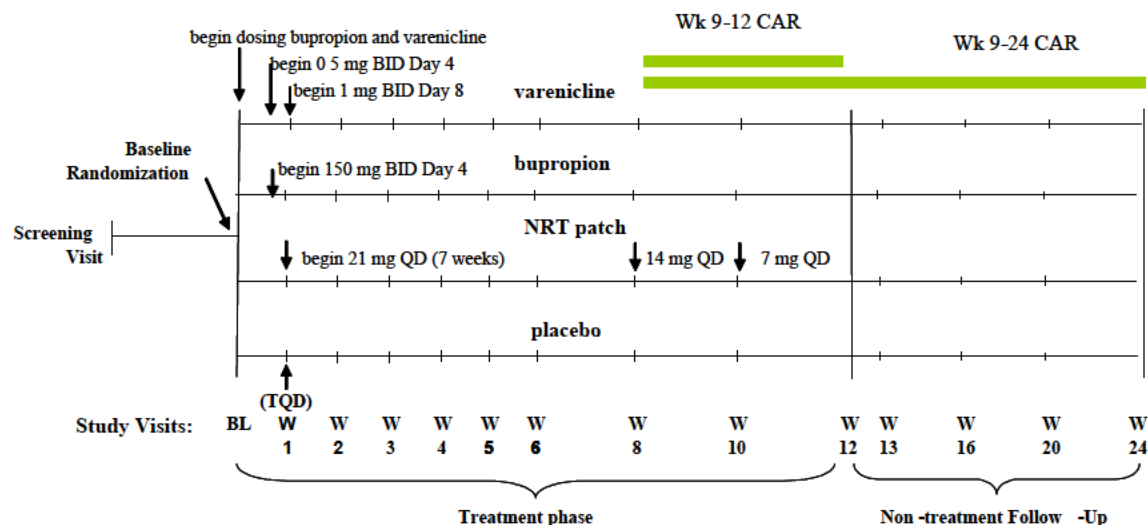
An additional secondary efficacy endpoint is the 7-day point prevalence of abstinence at each assessment visit.

## **3. STUDY DESIGN**

This is a 24-week, double-blind, NRT and placebo-controlled, multi-center, parallel group study designed to assess the safety and efficacy of varenicline 1 mg BID and bupropion hydrochloride 150 mg BID for smoking cessation. The primary comparisons will be varenicline vs. placebo and bupropion vs. placebo. NRT is included as active control and study medications will be given via a triple-dummy design. The duration of active treatment is 12 weeks followed by a non-treatment follow-up phase for an additional 12 weeks (see diagram below). The study will randomize approximately 2000 subjects in each of 4 treatment arms, for a total of 8000 subjects at approximately 200 sites.

Subjects will be classified into one of the two cohorts—those with an established and stable diagnosis of psychiatric disorder, confirmed by the Structured Clinical Interview for DSM-IV Axis 1 and 2 Disorders (SCID I and II) conducted at screening; and those without a diagnosis of psychiatric disorder. An equal number of subjects with or without a diagnosis of a psychiatric disorder will be enrolled and randomized among the 4 treatment arms (varenicline, bupropion, NRT, and placebo) in 1:1:1:1 ratio. All clinic visits are in an outpatient clinic setting.

## Study Diagram:



W = Week; BL = Baseline; TQD = Target quit date; CAR = Continuous abstinence rate

**Screening Phase:** The screening period will be approximately 3-14 days in duration. Results of screening laboratory evaluations and the electrocardiogram will be reviewed during this period to assure subject eligibility. Determination if there is a diagnosis of a psychiatric disorder for each subject will be confirmed at screening using DSM IV TR based on clinical assessment and confirmed by SCID I and II.

A subject who meets all inclusion criteria at the screening visit will progress to the baseline visit. At the baseline visit only those subjects who continue to meet all other criteria will be randomized.

**Treatment Phase:** The 12-week placebo controlled treatment period has periodic clinic visits for safety and efficacy assessments and smoking cessation counseling. There will be weekly clinic visits up to and including Week 6 and then biweekly clinic visits between Week 6 and Week 12. On weeks with no scheduled clinic visits, telephone contact visits will occur to collect smoking status. During the active treatment phase, varenicline and bupropion dosing will begin on the Baseline day with a one-week titration followed by 11 weeks of 1 mg BID and 150 mg BID respectively. NRT dosing will begin at the Week 1 visit with a 21 mg patch per day for 7 weeks, followed by a 14 mg patch per day for 2 weeks, and then a 7 mg patch for 2 weeks. All subjects will set a target quit date (TQD) to coincide with the Week 1 visit. The Week 1 visit occurs at the end of the first week of the treatment phase (Day 8). Smoking cessation counseling up to 10 min duration will be provided at each clinic visit consistent with the Agency for Healthcare Research and Quality (AHRQ) guidelines beginning at Baseline.



**Non-Treatment Phase:** Study drug will be discontinued at the Week 12 visit and subjects will continue into the non-treatment follow-up period. Clinic visits will occur at Weeks 13, 16, 20 and 24. On weeks with no scheduled clinic visits, telephone contact visits will occur to collect smoking status. Smoking cessation counseling up to 10 min duration will be provided at each clinic visit consistent with the Agency for Healthcare Research and Quality (AHRQ) guidelines.

#### **4. SUBJECT SELECTION**

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

##### **4.1. Inclusion Criteria**

Subject eligibility should be reviewed and documented by the Investigator before subjects are included in the study. Subjects both with and without a diagnosis of a major psychiatric disorder will be eligible for this study. Subjects without a diagnosis of a psychiatric disorder that meet all other study criteria are eligible to be included in the non-psychiatric stratum. To be included in the non-psychiatric stratum, the subject must not have ANY previous diagnosis of a psychiatric disorder confirmed by SCID I and II.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the psychiatric or non-psychiatric arm of the study:

1. Male or female cigarette smokers, 18-75 years, motivated to stop smoking and considered suitable for a smoking cessation attempt.
2. Smoked an average of at least 10 cigarettes per day during past year and during the month prior to the screening visit, and exhaled carbon monoxide (CO) >10 ppm at screening.
3. Females who are not of childbearing potential (ie, who are surgically sterilized or at least 2 years postmenopausal) and who are not nursing may be included. Females who are of childbearing potential may be included provided that they are not pregnant, not nursing, and meet all of the following criteria:
  - Are instructed and agree to avoid pregnancy through 30 days after the last dose of study medication;
  - Have a negative pregnancy test ( $\beta$ -hCG) at Screening and Baseline and
  - Agree to use at least one of the birth control methods listed below:

- An oral contraceptive agent, an intrauterine device (IUD), an implantable contraceptive (eg, Norplant), or an injectable contraceptive (eg, Depo Provera) for at least 1 month prior to entering the study and will continue its use through at least 30 days after the last dose of study medication or;
  - A double barrier method of contraception, eg, condom and diaphragm with spermicide while participating in the study through at least 30 days after the last dose of study medication or abstinence.
4. A personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
  5. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

#### **4.1.1. Additional Inclusion Criteria for Neuropsychiatric Cohort**

In addition to the criteria above, subjects to be included in the Neuropsychiatric cohort must also meet the following:

All subjects will be screened for Axis I and II diagnosis (current and/or past) using DSM IV TR criteria based on clinical assessment and confirmed by SCID (administered by a clinician<sup>1</sup> or a qualified person trained in clinical mental health, ie; a PhD level clinical psychologist, or an individual with master level training in related areas [masters level psychologist, social work] who have been trained to use the SCID<sup>2</sup>). A “current” diagnosis is defined as the subject meeting the established criteria in the prior month. A “past” diagnosis is also the same as a “lifetime” diagnosis where applicable. A past diagnosis can have occurred anytime in the past medical history. The four major diagnostic groups comprising the neuropsychiatric cohort are: Psychotic, Affective, Anxiety and Personality Disorders. The four diagnostic groups are further described below. Subjects will be included in the psychiatric cohort, if they are considered clinically stable and meet criteria, either current or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and have met diagnostic criteria before the initiation of study treatment.

a. Psychotic Disorders limited to:

- Schizophrenia;
- Schizoaffective.

b. Affective Disorders limited to:

- Major Depression;

---

<sup>1</sup> Clinician is defined as someone licensed to practice medicine according to existing regulations.

<sup>2</sup> Documentation of training will be kept at the clinical site.

- Bipolar-I;
- Bipolar-II.

c. Anxiety Disorders limited to:

- Panic Disorder with or without Agoraphobia;
- Post-Traumatic Stress Disorder;
- Obsessive-Compulsive Disorder;
- Social Phobia;
- Generalized Anxiety Disorder.

d. Personality Disorders limited to past history of:

- Borderline Personality Disorder.

All subjects with an Axis I or II diagnosis must be judged to be clinically stable including the following:

- No acute exacerbation of their condition in the preceding 6 months;
- If on treatment for their condition, must have been on stable treatment for a minimum of 3 months (eg, stable drug and dose  $\geq 3$  months);
- No change in treatment is anticipated for the duration of the study;
- In the opinion of the Investigator, the patient is not at high risk of self-injury or suicidal behavior;
- In the event the Investigator is not a mental health professional (MHP), the subject should be evaluated by a MHP to confirm the SCID I or II diagnosis and determine if the subject is stable. A MHP must be a psychiatrist or licensed PhD level clinical psychologist. **A subject who requires new treatment or is judged not to be clinically stable cannot be randomized.**

Subjects who did not meet study inclusion criteria may be re-screened if deemed clinically stable at a later date and the case has been reviewed and approved by the Pfizer clinician.

#### 4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects with a past or current diagnosis of one of the following disorders:

- a. Psychotic Disorders:
  - Schizophreniform;
  - Delusional Disorder;
  - Psychotic Disorder NOS.
- b. All Delirium, Dementia, and Amnesic and Other Cognitive Disorders;
- c. All Substance-Induced Disorders (Other than nicotine);
- d. All Factitious Disorders;
- e. All Dissociative Disorders;
- f. All Impulse Control Disorders;
- g. Evidence of substance abuse/misuse or dependence severe enough to compromise the subject's ability to comply with the study requirements;
- h. Subjects with antisocial, schizotypal, or any other personality disorder severe enough to compromise the subject's ability to comply with the study requirements.

Subjects with a past history of a comorbid condition listed in the above Exclusion Criteria may be included in the study and placed in the "psychiatric stratum" if A) the subject is concurrently diagnosed with an inclusionary diagnosis, B) the subject is able to comply with study requirements, and C) for substance abuse/misuse, the subject is considered to be in sustained full remission (no criteria for abuse or dependency being met in the last 12 months), and D) the patient is not taking agonists or partial agonists (ie, methadone, buprenorphine).

If the subjects described above (exclusionary co-morbid psychiatric condition) do not meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, they are not eligible for the study. Subjects who meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, and who have a co-morbid condition not listed in the protocol (for example, agoraphobia without history of panic attacks) may be eligible for inclusion in the psychiatric arm if in the opinion of the investigator the concurrent condition is stable and does not prevent the subject from safely complying with study procedures. In such cases, please consult with the medical monitor.

2. Subjects with an Axis I diagnosis according to DSM IV TR criteria who have a rating of 5 or higher on the Clinical Global Impression- Severity (CGI-S). [Appendix 7](#).

3. Subjects who are believed to have a suicidal risk at screening, baseline, or after assessment by a qualified MHP-(Psychiatrist or licensed PhD level clinical psychologist) if a risk assessment interview was required after screening or baseline using the Columbia Suicide Severity Rating Scale (C-SSRS). See section 7.1.2 ([Appendix 10](#)).
  - Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS. Appendix 10.
  - Previous history of suicide behaviors in the past year.
4. Subjects who in the opinion of the Investigator display self-injuring behaviors.
5. Subjects with a positive urine drug screen at screening or baseline for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition.
6. Subjects taking an investigational drug within 30 days before the Baseline visit and at anytime during the study period.
7. Subjects who have taken varenicline, bupropion, or NRT within 30 days prior to Baseline visit.
8. Only one subject per household may participate.
9. Subjects for whom treatment with bupropion is not appropriate:
  - Subjects with seizure disorder;
  - Subjects undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines);
  - Subjects with current or prior diagnosis of anorexia or bulimia nervosa;
  - Subjects who have taken a monoamine oxidase (MAO) inhibitor within the past fourteen days (prior to the Baseline visit);
  - Subjects who are taking the following narrow therapeutic range medications which are metabolized by CYP2D6; desipramine, nortriptyline, Type 1C antiarrhythmics (eg, propafenone, flecainide), thioridazine.

Specific information regarding warnings, precautions, contraindications, adverse events and other pertinent information on bupropion that may impact subject eligibility is provided in the Core Data Sheets. In particular, bupropion should be administered with extreme caution to patients with risk factors for seizures, eg, a history of seizure, cranial trauma, or concomitant medications that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic steroids, etc.).

10. Subjects who intend to donate blood or blood components while receiving study drug or within 1 month of the completion of the treatment phase of the study.
11. Subjects with severe chronic obstructive pulmonary disease (COPD) defined as any subject who fulfills any of the following criteria:
  - History of repeated exacerbations of COPD (greater than or equal to 3 in 3 years);
  - Requires systemic corticosteroid maintenance (eg, oral prednisolone) for management of chronic symptoms;
  - Is maintained on oxygen therapy for management of chronic symptoms.
12. Subjects with a recent (<5 years) history of cancer. Subjects with a remote (>5years) history of cancer may be considered pending discussion with the study clinician. Subjects with cured basal cell or squamous cell carcinoma of the skin are allowed.
13. Subjects with evidence or history of clinically significant allergic reactions to drugs (eg, severe cutaneous and/or systemic allergic reactions).
14. Any subject at screening with an SGOT (AST) or SGPT (ALT) greater than 3 times the upper limit of normal (ULN) or total bilirubin greater than 2 times the ULN.
15. Subjects with clinically significant cardiovascular disease in the past 2 months. Examples of clinically significant cardiovascular disease include:
  - Myocardial infarction;
  - Coronary artery bypass graft (CABG);
  - Percutaneous transluminal coronary angioplasty (PTCA);
  - Severe or unstable angina;
  - A serious arrhythmia;
  - Clinically significant ECG conduction abnormalities;
  - Hospitalizations for heart failure.
16. Subjects with clinically significant cerebrovascular disease in the past 2 months. Examples of clinically significant cerebrovascular disease include:
  - Cerebrovascular accident (CVA), stroke;
  - Documented transient ischemic attack (TIA).

17. Subjects who do not agree to abstain from using non-cigarette tobacco products (including, eg, pipe tobacco, cigars, snuff, chewing tobacco, hookah, etc.) or marijuana during study participation.
18. Subjects who do not agree to abstain from using nicotine replacement therapy, bupropion, varenicline and other aids to smoking cessation during study participation (both the treatment phase and the post-treatment follow-up).
19. Subjects who have previously experienced an adverse drug reaction that the investigator considers potentially due to treatment with any of the active drugs in this study and of sufficient concern that further exposure to this medication would be inadvisable.
20. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
21. Subjects taking a concomitant medication that is prohibited by this protocol (See Section 5.5).
22. Subjects with skin conditions resulting in red, broken or irritated skin that may hinder the use of the nicotine replacement therapy (NRT) patch.

#### **4.3. Randomization Criteria**

Subjects who meet inclusion and exclusion criteria may be randomized. A computer-generated randomization schedule will be used to assign subjects to treatment, with two-level stratification by the presence or absence of a diagnosis of psychiatric disorder. An equal number of smokers will be enrolled in each of the two cohorts. When the planned enrollment has been achieved in one of the cohorts, enrollment will continue only into the other cohort until recruitment goals have been reached.

Within the cohort with a diagnosis of a psychiatric disorder, treatment assignment will be stratified with respect to the four major diagnosis groups (Psychotic, Affective, Anxiety and Personality Disorders).

#### **4.4. Life Style Guidelines**

Participants are expected to abstain from the use of tobacco products such as pipe tobacco, cigars, snuff, chewing tobacco, hookah, and the use of marijuana. Subjects will be expected to refrain from using any form of nicotine replacement therapy, bupropion, varenicline and other aids to smoking cessation during both the treatment and non treatment follow-up phases.

Females of childbearing potential (not surgically sterilized or <2 years postmenopausal) must agree to practice a form of effective contraception, such as an oral contraceptive agent, an intrauterine device (IUD), an implantable contraceptive (eg, Norplant), or an injectable contraceptive (eg, Depo Provera) for at least 1 month prior to entering the study and will continue its use through at least 30 days after the last dose of study medication. Alternatively they may use double barrier contraception (ie, condom plus spermicide in combination with a female condom, diaphragm, cervical cap or intrauterine device), or sexual abstinence prior to entering into the study and for at least 30 days following the last dose of study drug.

## 5. STUDY TREATMENTS

This study utilizes a triple-dummy design as shown in the table below. Subjects randomized to one of the three active dosing groups will take that active medication and the other 2 medications in matching placebo form. And subjects randomized to placebo will receive matching placebo for varenicline, bupropion, and NRT, and follow the same titration and dosing schedules as those randomized to each of the active medication groups.

Treatment group	Day 1-3	Day 4-7	Week 1*-8	Week 8-10	Week 10-12
Varenicline (V)	0.5 mg V QD 1 placebo B QD	0.5 mg V BID 1 placebo B BID	1 mg V BID 1 placebo B BID 1 placebo NRT QD	1 mg V BID 1 placebo B BID 1 placebo NRT QD	1 mg V BID 1 placebo B BID 1 placebo NRT QD
Bupropion (B)	150 mg B QD 1 placebo V QD	150 mg B BID 1 placebo V BID	150 mg B BID 1 placebo V BID 1 placebo NRT QD	150 mg B BID 1 placebo V BID 1 placebo NRT QD	150 mg B BID 1 placebo V BID 1 placebo NRT QD
NRT patch	1 placebo V QD 1 placebo B QD	1 placebo V BID 1 placebo B BID	21mg NRT QD 1 placebo V BID 1 placebo B BID	14 mg NRT QD 1 placebo V BID 1 placebo B BID	7 mg NRT QD 1 placebo V BID 1 placebo B BID
Placebo	1 placebo V QD 1 placebo B QD	1 placebo V BID 1 placebo B BID	1 placebo V BID 1 placebo B BID 1 placebo NRT QD	1 placebo V BID 1 placebo B BID 1 placebo NRT QD	1 placebo V BID 1 placebo B BID 1 placebo NRT QD

\*On day of Week 1 visit, the varenicline dose will be taken as 2-0.5 mg tablets (or 2 placebo varenicline tablets) in the AM and 1 mg tablet (or 1 placebo varenicline tablet) in the PM.

All subjects randomized to varenicline will be titrated to the full dose during the first week in the following manner: 0.5 mg QD x 3 days, 0.5 mg BID x 4 days, then 1 mg BID for 11 weeks. Subjects randomized to bupropion will receive 150 mg QD x 3 days and then will take 150 mg BID for the remainder of the treatment period (11 weeks and 4 days). Subjects randomized to NRT will start active dosing the morning of the Week 1 visit and will receive a 21 mg transdermal patch per day x 7 weeks, followed by a 14 mg transdermal patch per day x 2 weeks, and then a 7 mg transdermal patch x 2 weeks for a total of 11 weeks of treatment.

Dosing will continue until the Week 12 visit. All subjects will then be followed for an additional 12 weeks in the non-treatment phase of the protocol.



Smoking cessation counseling of up to 10 minutes will be given at each clinic visit during the treatment and non-treatment periods. The counseling will be 1:1, individually tailored to each subject's needs, and consistent with AHRQ guidelines. Whenever possible, counseling should be conducted by the same counselor throughout, so that the relationship builds and brings additional value to the sessions.

### **5.1. Allocation to Treatment**

This is a double-blind, parallel group study. Subjects will be stratified by diagnosis of psychiatric disorder or lack thereof and then randomized to varenicline, bupropion, NRT or placebo in a 1:1:1:1 ratio. Overall enrollment will be equal for the two cohorts (and within the cohort with a diagnosis of psychiatric disorder, treatment will be balanced with respect to the major diagnosis groups, per Section 4.3). Investigators will obtain subject identification numbers and study drug assignments utilizing a web-based or telephone call-in drug management system as directed by the sponsor. Identification numbers for the subjects will be provided at the screening visit.

### **5.2. Breaking the Blind**

The study will be subject, investigator, and sponsor blinded.

At the initiation of the study, the study site will be instructed on the method for breaking the blind of an individual subject. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented.

### **5.3. Drug Supplies**

#### **5.3.1. Formulation and Packaging**

Blinded tablets (varenicline, bupropion, or placebo) will be supplied in bottles containing sufficient tablets to dose daily between visits during the treatment period. Varenicline will be supplied as 0.5 mg tablets for the first week and 1.0 mg tablets for the remaining 11 weeks of the study treatment period. Bupropion will be supplied as 150 mg tablets. Blinded NRT (active and placebo) will be supplied in cartons containing sufficient transdermal patches to cover each study visit schedule, 21 mg patch for Weeks 1 to 8, 14 mg patch for Weeks 8 to 10, and 7 mg patch for Weeks 10 to 12. New bottles and cartons will be dispensed at each clinic visit to provide sufficient study drug until the next scheduled clinic visit.

#### **5.3.2. Preparation and Dispensing**

Study drug is to be dispensed to subjects by qualified site study staff at each scheduled clinic visit from the Baseline visit to the Week 10 visit (according to the study flowchart). Subjects will be given their first supply of bottles at the Baseline visit and first supply of patches at the Week 1 visit and will receive new supplies at each clinic visit through the Week 10 visit.

Subjects will be instructed to store the study drug at room temperature (20-25°C or 69-77°F) and out of the reach of children.

All empty or unused study medication (bottles and patches) must be returned by each subject at each clinic visit through Week 12. Unused medication will be catalogued by site staff to verify data reported by the subjects.

### **5.3.3. Administration**

Varenicline (or placebo) administration will begin with a titration period. Treatment will begin from the Week 1 bottle on the evening of the Baseline visit day. For the first 3 days of the Week 1 dosing period subjects will take one 0.5 mg tablet per day in the evening. For the next 4 days this will increase to two 0.5 mg tablets per day, 1 in the morning and 1 in the evening. On the day of the Week 1 visit (Day 8), subjects will increase their dose to two 0.5 mg tablets in the morning. At the Week 1 visit and subsequent clinic visits through the Week 10 visit subjects will receive new bottles and will take two 1 mg tablets daily, one in the evening and one in the morning.

Bupropion (or placebo) administration will begin with a titration period. Treatment will begin from the Week 1 bottle on the evening of the Baseline visit day. For the first 3 days of the Week 1 dosing period subjects will take one 150 mg bupropion in the evening. On Day 4 they increase dosing to one 150 mg bupropion BID (one in the morning and one in the evening) and dosing remains unchanged until Week 12.

Dosing should occur with 240 ml of water and it is recommended that subjects eat prior to dosing. It is recommended that there be at least 8 hours between the morning and evening dosing.

At the discretion of the Investigator, dosing with blinded tablet medications (varenicline, bupropion, matching placebos) may be reduced, temporarily discontinued or stopped for subjects who have intolerable adverse events (eg, nausea); or for subjects who in the opinion of the Investigator require a dose reduction due to use of concurrent medications. A dose reduction is performed by decreasing both blinded tablet medications to once per day dosing. If a dose reduction is required, both blinded tablet medications should be reduced at the same time.

NRT (or placebo) administration starts on the day of the Week 1 visit and subjects will receive a 21 mg transdermal patch per day for 7 weeks, followed by a 14 mg transdermal patch per day for 2 weeks, and then a 7 mg transdermal patch for 2 weeks for a total of 11 weeks of treatment.

At the discretion of the Investigator, dosing with blinded NRT (NRT or matching placebo) may be temporarily discontinued or stopped for subjects who have intolerable adverse events. It is not possible to reduce the dose of blinded NRT.

If any of the study drugs need to be permanently discontinued then all 3 blinded study medications (varenicline/placebo, bupropion/placebo, and NRT/placebo) must be permanently discontinued.

Medication errors may result in this study from the administration or consumption of the wrong study drug or by the wrong study subject. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the CRF and on the SAE form when appropriate. In the event of a medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page (refer to [ADVERSE EVENT REPORTING](#) section for further details).

#### **5.3.4. Compliance**

Subjects will return bottles and cartons at each clinic visit and a drug accountability form will be completed. Missed doses should be discussed to try to ascertain the reason(s). Reasons for missed doses and/or patterns of missed doses should be incorporated into the smoking cessation counseling and every effort should be made to ensure proper subject dosing.

#### **5.4. Drug Storage and Drug Accountability**

The investigator or an approved representative (eg, pharmacist), will ensure that all study drug is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Store at room temperature as indicated on the label.

To ensure adequate records, all study drug will be accounted for in drug accountability inventory forms as instructed by Pfizer. Subjects must return all bottles and cartons to the investigator. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies must be returned to Pfizer or its designated agent.

#### **5.5. Concomitant Medication(s)**

While medications with narrow therapeutic index that are metabolized by CYP 2D6 are excluded (please refer to Any Use Prohibited, below), there is the potential for increased blood levels of certain antipsychotic and antidepressant medications. Therefore, investigators should pay attention to signs and symptoms of increased blood levels, and if noted, call the medical monitor for advice on how to manage the subject. These signs and symptoms should be recorded as adverse events.

If investigators have questions on any drugs not listed here they should be discussed with the study clinician.

Episodic Use Only Permitted:

- Acetaminophen;
- Antihistamines;
- Aspirin (chronic use also permitted);
- Bronchodilators (chronic use also permitted);
- Inhaled steroids (chronic use also permitted);
- Oral and injectable steroids;
- Nitroglycerin;
- COX-2 selective and non-selective NSAIDs (chronic use also permitted);
- Over the counter medications (excluding stimulants, Kava Kava, St. John's Wort).

Chronic Use Permitted:

- Anti-anginal agents;
- Antihypertensive agents;
- Antidepressants, Antipsychotics, Anxiolytics, and Mood stabilizer treatments prescribed for an Axis I disorder (Except for Tricyclic antidepressants, Thioridazine and Bupropion as described below);
- Aspirin;
- Bronchodilators;
- Hormone Replacement Therapy;
- Inhaled steroids;
- Lipid-lowering agents;
- Multivitamins;
- COX-2 selective and non-selective NSAIDs;

- Oral and depot contraceptives;
- Thyroid replacement;
- Oral diabetes medications.

Any Use Prohibited:

- Drugs containing bupropion ;
- Varenicline (Chantix®/Champix®);
- Nicotine replacement therapy and other aids to smoking cessation;
- Naltrexone;
- Insulin;
- Theophylline;
- Warfarin;
- Monoamine oxidase (MAO) inhibitors;
- Over the counter and prescribed stimulants and anorectic agents;
- Narrow therapeutic range medications which are metabolized by CYP2D6; desipramine, nortriptyline, Type 1C antiarrhythmics (eg, propafenone, flecainide), thioridazine;
- Milnacipran (Scavella).

## **6. STUDY PROCEDURES**

### **6.1. Screening**

The Screening visit will occur 3 to 14 days prior to the baseline/randomization. The following procedures will be conducted during screening:

- Obtain informed consent for the clinical trial (must be signed prior to the initiation of any study related activities);
- Record demography, medical history, cardiovascular medical history, and smoking history (including questions regarding past attempts to quit smoking, cigarette use, assessment of past and present illicit drug use, an assessment of past and present alcohol use, and past use of NRT, bupropion and varenicline);

- Physical examination;
- Measure and record height;
- Complete the Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID I and II). The SCID II consists of a subject- completed Personality Questionnaire and follow up Interview-based questions;
- In the event the Investigator is not a mental health professional (MHP), the subject should be evaluated by a MHP to confirm the SCID I or II diagnosis and determine if the subject is stable. A MHP must be a psychiatrist or licensed PhD level clinical psychologist. **A subject who requires new treatment or is judged not to be clinically stable cannot be randomized;**
- Complete the Clinical Global Impression- Severity (CGI-S) [Appendix 7](#);
- Subject completes the Suicidal Behaviors Questionnaire-Revised (SBQ-R) [Appendix 3](#);
- Complete the Columbia Suicide Severity Rating Scale (C-SSRS) [Appendix 10](#);
- Record concomitant medications and non- drug treatment;
- Subject completes the Fagerström Test for Nicotine Dependence<sup>6</sup> [Appendix 1](#);
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Record a 12-lead electrocardiogram (ECG);
- Collect blood samples for CBC and blood chemistry;
- Perform urine or serum pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal;
- Perform urine drug screen (dipstick at site);
- Verify trial eligibility by checking and documenting Inclusion/Exclusion criteria; [4.1](#), [4.2](#).
- Psychiatric evaluation if warranted (See Section [7.1.10](#)).

Subjects who did not meet study inclusion criteria may be re-screened if deemed clinically stable at a later date and the case has been reviewed and approved by the Pfizer clinician.

## 6.2. Study Period

### 6.2.1. Baseline Visit (Randomization)

The following procedures will be conducted at the Baseline visit:

- Record sitting blood pressure, pulse rate and weight;
- Review cardiovascular medical history and update as needed;
- Record volunteered adverse events;
- Complete CGI-S [Appendix 7](#);
- Subject completes the Hospital Anxiety and Depression Scale (HADS) [Appendix 2](#);
- Complete Aggression Questionnaire [Appendix 5](#);
- Conduct Neuropsychiatric Adverse Events Interview and record solicited adverse events [Appendix 6](#);
- Record concomitant medications and non- drug treatment;
- Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) [Appendix 10](#) and record suicide-related adverse events;
- Complete the Nicotine Use Inventory (NUI) [Appendix 4](#);
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Perform urine drug screen (dipstick at site);
- Perform pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal (dipstick at site);
- Provide subject with study specific Emergency Contact Information Card;
- Smoking Cessation counselling 1:1 ≤10 minutes;
- Re-check and document Inclusion/Exclusion criteria; see Section [4.1](#), [4.2](#);
- Randomize to treatment;
- Dispense study drug: Baseline bottles of study drug;
- Psychiatric evaluation if warranted (See Section [7.1.10](#)).

### 6.2.2. Clinic Visits (Week 1 to 6 Visits, Weeks, 8, 10, 12 and ET<sub>12</sub> Visit)

One week after their Baseline visit the subject will return for the Week 1 visit. The Week 1 visit should occur on study Day 8 and will be planned to coincide with the day on which the subject will attempt to quit, called the target quit date (TQD). The subject's last cigarette prior to the quit attempt will be before midnight prior to the Week 1 visit.

Following the Week 1 visit, clinic visits will be conducted weekly at Weeks 2, 3, 4, 5, 6 and then bi-weekly at Weeks 8, 10, and 12. Every effort should be made to have the subject return on the same day of the week for the clinic visits, thereby keeping visits on time. To accommodate unforeseen circumstances a visit window of  $\pm 3$  days can be allowed throughout the study as long as proper dosing is maintained in the dosing period. The visit window should be used with discretion and all subjects should remain on original visit schedule throughout study participation (ie, If weekly visits were previously conducted on Wednesdays, the visits should return to Wednesdays after the window is utilized). If an early termination occurs before the end of Week 12, an early termination visit (ET<sub>12</sub>) will be conducted. It should be noted that these ET visits relate only to early termination in the study not early stopping of treatment, which is a situation where the subject should be encouraged to continue study participation to complete the remaining scheduled visits through Week 24. At each of these visits, the following procedures will be conducted:

- Record sitting blood pressure and pulse rate;
- Record volunteered adverse events;
- Complete CGI-I [Appendix 8](#);
- Subject completes the HADS [Appendix 2](#);
- Conduct Neuropsychiatric Adverse Events Interview and record solicited adverse events [Appendix 6](#);
- Record concomitant medications and non-drug treatment and update existing concomitant medications as needed;
- Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) [Appendix 10](#) and record suicide-related adverse events;
- Complete the Nicotine Use Inventory (NUI) [Appendix 4](#);
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Perform pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal;
- Smoking Cessation counseling 1:1  $\leq 10$  minutes;



- Dispense drug bottles and patches sufficient until next clinic visit (not at Week 12 or ET<sub>12</sub>);
- Subjects who report severe neuropsychiatric AEs or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) or answer "yes" to items 4, 5 or any suicidal behavioural question on C-SSRS appendix 10 will receive a psychiatric evaluation by a qualified mental health professional (MHP: psychiatrist or licensed PhD level clinical psychologist).
- Collect and forward records on cardiovascular events of interest or hospitalizations as defined in [Appendix 12](#) for adjudication, if applicable.

**Additional procedures at Week 12 visit or ET<sub>12</sub> visit.**

- Record a 12-lead electrocardiogram (ECG);
- Record sitting blood pressure and pulse rate;
- Measure and record weight;
- CBC, blood chemistry.

**6.2.3. Telephone Visits (Weeks 7, 9, 11)**

Complete the Nicotine Use Inventory (NUI). [Appendix 4](#).

**6.3. Nontreatment Follow-up Period (Weeks 13 through 24)**

Following completion of the Week 12 visit, subjects will continue into the non-treatment follow-up phase of the protocol. If a subject discontinues study drug prior to the Week 12 visit, the subject should be encouraged to continue study participation to complete the remaining scheduled visits through Week 24.

**6.3.1. Clinic Visits (Weeks 13, 16, 20, 24 and ET<sub>24</sub> Visit)**

Subjects will return for visits to the clinic at the end of Weeks 13, 16, 20, and 24. If an early termination occurs after the Week 12 visit and before the Week 24 visit, an early termination visit (ET<sub>24</sub>) will be conducted. At these visits, the following procedures will be conducted:

- Record sitting blood pressure and pulse rate;
- Record Body Weight (Week 24 and ET<sub>24</sub> only);
- Record volunteered adverse events;
- Complete CGI-I; [Appendix 8](#)

- Subject completes the HADS; [Appendix 2](#);
- Conduct Neuropsychiatric Adverse Events Interview (NAEI) and record solicited adverse events [Appendix 6](#);
- Record concomitant medications and non- drug treatment and update existing concomitant medications as needed;
- Complete the Columbia Suicide-Severity Rating Scale (CSSRS) [Appendix 10](#) and record suicide-related adverse events;
- Complete the Nicotine Use Inventory (NUI) [Appendix 4](#);
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Perform pregnancy test for all females unless surgically sterilized or at least 2 years postmenopausal at Week 16;
- Smoking Cessation counseling 1:1 ≤10 minutes;
- Subjects who report severe neuropsychiatric AEs or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) or who answer "yes" to items 4, 5 or any behavioural question on CSSRS [Appendix 10](#) will receive a psychiatric evaluation by a qualified mental health professional (MHP: psychiatrist or licensed PhD level clinical psychologist).
- Collect and forward records on cardiovascular events of interest or hospitalizations as defined in [Appendix 12](#) for adjudication, if applicable.

#### **6.3.2. Telephone Visits (Weeks 14, 15, 17, 18, 19, 21, 22, and 23)**

- Complete the Nicotine Use Inventory (NUI). [Appendix 4](#).

#### **6.4. Subject Withdrawal**

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

Subjects who discontinue treatment will be encouraged to continue participation in the study and all planned assessments/evaluations. Specifically, they will maintain the visit schedule and should continue participation through the non-treatment follow-up phase of the study.

All subjects who permanently discontinue study drugs for any reason should remain in the study as Off Treatment and In Study (OTIS). Every effort should be made to keep the subject in the study until the final visit and all planned assessments/evaluations should be performed. Specifically, the subject will maintain the visit schedule and continue participation through the non-treatment follow-up phase of the study.

If a subject withdraws from the study, but does not withdraw consent, he/she should be contacted at the end of the trial to assess vital status/cardiovascular events. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. All reasonable efforts should be made to contact subjects who are lost to follow up to ascertain their reason(s) for not continuing in the study. A determination needs to be made that they are truly lost to follow up and not withdrawing for another reason (eg, adverse event or lack of efficacy).

#### **6.4.1. Individual Subject Dosing Stopping Criteria**

During the double-blind, active treatment phase subjects will be monitored on a regular basis for any clinically significant symptomatic changes, including any changes in neuropsychiatric symptoms. The following individual dosing stopping criteria will be followed:

Dosing with blinded tablet medications (varenicline, bupropion, matching placebos) may be reduced, temporarily discontinued or stopped for intolerable adverse events, or if the Investigator believes that continuing dosing will be detrimental to the subject's mental or physical health.

Dosing with blinded NRT (NRT or matching placebo) may be temporarily discontinued or stopped for intolerable adverse events or if the Investigator believes that continuing dosing will be detrimental to the subject's mental or physical health. It is not possible to reduce the dose of blinded NRT.

- If a subject answers "yes" on items 4, 5 or to any behavioral question on the CSSRS, [Appendix 10](#) the subject must have a risk assessment by a qualified mental health professional (MHP: Psychiatrist or licensed PhD level clinical psychologist) to determine whether it is safe to continue active dosing in trial. In the event the risk assessment can not be immediately performed, it will be at the discretion of the Investigator to determine if study drug should be discontinued (temporarily or permanently) until the risk assessment is completed.
- Study drug will be discontinued immediately for any female subject who becomes pregnant during the treatment period of the study. These subjects should continue to attend study visits OTIS as noted in Section [6.4](#)

## 7. ASSESSMENTS

### 7.1. Safety

#### 7.1.1. Adverse Events

All adverse events (AEs) volunteered, observed, or solicited (of all severities) will be recorded in the AE CRF from the time the subject signs the informed consent up to and including Week 24.

Solicited neuropsychiatric adverse events will be collected by use of the Neuropsychiatric Adverse Event Interview (NAEI) at each clinic visit (starting from baseline) up to and including Week 24. The voluntarily reported AEs will be assessed first at each study visit followed by the NAEI [Appendix 6](#) and then the CSSRS [Appendix 10](#).

When reporting an adverse event, verbatim text will also be recorded on a supplemental adverse event reporting page. Reported events by a household member of the subject or personal physician, which are deemed to be adverse events by the Investigator, will be captured as adverse events and the reporters' verbatim text of these events will also be captured.

Suicide related adverse events will be solicited by completion of the C-SSRS at each clinic visit up to and including Week 24. Any severe neuropsychiatric adverse event(s) or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) recorded will require the subject to receive a psychiatric evaluation by a qualified mental health professional MHP (Psychiatrist or licensed PhD level clinical psychologist) (Section [7.1.10](#)) and a narrative will be constructed for each event. In the event the investigator meets the requirements of the MHP, he/she may complete this evaluation.

Subjects will be provided with study specific Emergency Contact Information cards at the baseline visit. The card will state that the subject has made a commitment to stop smoking and has joined the study and seeks the help and support of the family at home. It will state the list of neuropsychiatric events of concern and encourage the family to call the site to report such events if the subject himself/herself seems unaware. If the subject consents, an additional card will be provided for the subject's PCP. In this manner, household members and PCPs will be alerted to the possibility of adverse events and provided with direct contact information for study site personnel.

##### 7.1.1.1. Primary Neuropsychiatric Safety Endpoint

The primary safety endpoint is the occurrence of at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide.

Thus, the adverse event database will include items having been captured by any of the following means:

- Volunteered adverse event reporting;
- Actively solicited neuropsychiatric adverse events through the conduct of the Neuropsychiatric Adverse Event Interview (NAEI) [Appendix 6](#) deemed to be adverse events by the Investigator;
- Items captured from proxy report (ie, PCP, family member) judged to be adverse events by the Investigator;
- Suicide related events solicited by completion of the C-SSRS [Appendix 10](#) and deemed to be an adverse event by the Investigator.

The primary safety endpoint encompasses events reported (via the AE CRF page) through any of the above means of assessments. Additionally, the MedDRA version and Preferred Terms to be included in the primary safety endpoint will be described in the Statistical Analysis Plan.

Secondary safety endpoint related to adverse events is the occurrence of the components of the primary safety endpoint.

#### **7.1.1.2. Actively Solicited Neuropsychiatric Adverse Events**

The Neuropsychiatric Adverse Event Interview (NAEI) [Appendix 6](#), will actively inquire about the following type of adverse events: aggression, anxiety, agitation, depression, delusions, dissociative states, feeling abnormal, hallucinations, homicidal ideation, hostility, mania, paranoia, panic, and psychosis. The NAEI, developed by Pfizer, was piloted in a similar population to the one to be included in this study (patients with and without a history of psychiatric disease enrolled in a smoking cessation program) to evaluate patient understanding of all questions. The results of the study support use of the NAEI for neuropsychiatric adverse events solicitation.

If a subject has a positive response to any item on the NAEI, a determination will be made by the investigator as to whether this meets criteria for an adverse event. If it does meet criteria as an adverse event it will be recorded on the adverse event pages of the Case Report Form.

#### **7.1.2. Columbia Suicide Severity Rating Scale (C-SSRS) [Appendix 10](#), and the Suicidal Behaviors Questionnaire (SBQ-R) [Appendix 3](#)**

The C-SSRS will be completed by trained site personnel at screening and at each subsequent clinic visit up to and including Week 24. The Suicidal Behaviors Questionnaire- Revised (SBQ-R) will be completed by the subject at the screening visit.

At the screening visit, to detect possible suicidality, the C-SSRS and SBQ-R are completed. A risk assessment will be done by a qualified mental health professional (MHP: Psychiatrist or licensed PhD level clinical psychologist) if the subject's responses on either of these screening instruments indicate:

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS; [Appendix 10](#).
- Previous history of suicide behaviors in the past year;
- In the investigators judgment a risk assessment is required.

At post-baseline visits during the study if subject answers "yes" on items 4, 5 or on any suicidal behavioral question on C-SSRS ([Appendix 10](#)) a risk assessment will be done by a qualified MHP to determine whether it is safe to continue active dosing in trial.

#### **7.1.3. Hospital Anxiety and Depression Scale (HADS) [Appendix 2](#)**

The HADS is a subject self-report scale and contains 14 items rated on 4-point Likert-type scales. Two subscales assess depression and anxiety.

If a subject scores  $\geq 11$  on the Depression subscale of the HADS at baseline or any time during the study, the subject should receive an evaluation by a MHP (see section [7.1.10](#)).

Subjects' self report via the HADS is aimed to more fully characterize potential depression and anxiety related events. These additional measurements will be collected and evaluated in a different manner than the observed or volunteered adverse events. No attempt will be made to resolve any apparent discrepancies between observed or volunteered adverse events and the additional data collected from subjects using the HADS self-report. These additional data will be presented in separate tables, separate figures, and separate data listings, and will be reviewed in the final study report.

#### **7.1.4. Clinical Global Impression of Severity (CGI-S) [Appendix 7](#)**

The CGI-S is a clinician rated instrument measuring the severity of a subject's psychiatric condition on a 7 point scale at time of assessment, relative to clinician's past experience in patients with same diagnosis. The scores are: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; or 7=extremely ill. The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as "Normal, not at all ill" on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as "No change" on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician's experience with the psychiatric population to which the subject belongs. This scale should be administered by the same rater throughout the study whenever possible.

#### **7.1.5. Clinical Global Impression of Improvement (CGI-I) [Appendix 8](#)**

The CGI-I is a clinician rated instrument that measures change in subject's psychiatric condition (or lack thereof in the stratum without psychiatric disorders) on a 7 point scale ranging from 1 (very much improved) to 7 (very much worse). The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as "Normal, not at all ill" on the CGI-S at baseline and assuming no psychiatric symptoms emerge during the trial, would be rated as "No change" on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician's experience with the psychiatric population to which the subject belongs. This scale should be administered by the same rater throughout the study whenever possible.

#### **7.1.6. Aggression Questionnaire (AQ) [Appendix 5](#)**

The Aggression Questionnaire is a subject self-reported scale and consists of 4 factors, Physical Aggression (PA), Verbal Aggression (VA), Anger (A) and Hostility (H), measured only at baseline for use as an historical benchmark. The total score for Aggression is the sum of the factor scores.<sup>1</sup>

#### **7.1.7. Nicotine Use Inventory (NUI) [Appendix 4](#)**

The Nicotine Use Inventory (NUI) is a questionnaire regarding use of cigarettes and other nicotine-containing products during the treatment period or tobacco products during non-treatment follow-up period. The NUI was designed for and applied in previous varenicline studies. The NUI will be completed weekly at all clinical visits and telephone contacts.

#### **7.1.8. End-Expiratory Exhaled Carbon Monoxide (Exhaled CO)**

In order to confirm the smoking abstinence reported in the NUI, an end-expiratory exhaled carbon monoxide (exhaled CO) will be measured at each clinic visit using a breath CO monitor. An exhaled CO  $\leq 10$  ppm is required to claim successful smoking cessation.

#### **7.1.9. Fagerström Test for Nicotine Dependence**

The Fagerström Test for Nicotine Dependence provides a short, self-reported measure of dependency on nicotine. This test will be completed at screening only. The test's questions and scale are shown in [Appendix 1](#).

#### **7.1.10. Psychiatric Evaluations/Risk Assessments**

A risk assessment should be done by a qualified mental health professional (MHP: a psychiatrist or licensed PhD level clinical psychologist) if any of the following conditions are met:



- If a subject reports a severe neuropsychiatric adverse event (as detailed in Section 2.2.1) or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) the subject will be referred for a psychiatric evaluation;
- Subject answers “yes” on item 5, on C-SSRS during the screening visit or subject answers “yes” on item 4, 5 or on any suicidal behavioral question on C-SSRS [Appendix 10](#) during the study;
- Previous history of suicide behaviors in the past year (prior to randomization);
- The subject scores  $\geq 11$  on the Depression subscale of the HADS [Appendix 2](#) at baseline or at any time during the study.

The investigator may also refer a subject for a psychiatric evaluation if they have concerns over their subject’s psychiatric condition at any other stage during the study.

The following items will be addressed in each evaluation:

- Is a therapeutic intervention required for the subject?
- Arrangement for treatment and follow-up as appropriate if a therapeutic intervention is required;
- Is this a new DSM IV diagnosis for this subject or an exacerbation of a pre-existing condition?

The evaluation will be done by a qualified mental health professional (MHP: Psychiatrist or licensed PhD level clinical psychologist). In the event the Investigator is also qualified as a MHP, he or she may conduct this evaluation. A written copy of the risk assessment should be included in the subject’s clinical record as source document and will be recorded in the case report form. Subjects who have a “yes” response on items 4, 5 or on any suicidal behavioral question on C-SSRS on more than one occasion during a study must have their potential suicidality managed appropriately by the Investigator together with a qualified MHP (or the Investigator alone if the Investigator is a qualified MHP). The subjects can continue dosing while being evaluated, at the Investigator’s discretion. In addition, the Investigator should consult with the Pfizer clinician to determine whether the subject can continue in the study.

#### **7.1.11. Psychiatric Treatment Monitoring**

At each clinic visit up to and including Week 24, any requirement for either a change in treatment or an initiation of treatment for an Axis I or II disorder (either drug therapy or psychotherapy) will be recorded.



#### **7.1.12. Physical Examination, Vital Signs and Electrocardiogram**

A physical examination will be performed at the screening visit. Abnormal changes from screening deemed clinically significant by the Investigator should be recorded as adverse events.

Body weight will be measured at the baseline visit and Wk 12 or ET<sub>12</sub> and Wk 24 or ET<sub>24</sub>. Height will be measured at the Screening visit. Both will be measured in indoor clothing without shoes.

Sitting blood pressure and pulse rate will be measured at the baseline visit, Wks 1, 2, 3, 4, 5, 6, 8, 10, Wk 12 or ET<sub>12</sub>, and Wks 13, 16, 20 and 24 or ET<sub>24</sub>. Blood pressure will be measured by an appropriate automated/semi-automated or manual sphygmomanometer and recorded to the nearest mmHg. All blood pressure measurements are to be taken in the dominant arm with the appropriate size cuff. Pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

A 12-lead electrocardiogram will be obtained at screening and at the end of treatment study visit (Wk 12 or ET<sub>12</sub>).

#### **7.1.13. Medical History**

Medical history, which comprises all past and present diseases or syndromes that in the Investigator's judgment are considered to be clinically significant, will be recorded in the CRF. This includes recording any significant cardiovascular, respiratory, endocrine/metabolic, gastrointestinal, genitourinary, musculoskeletal, hematological, neurological, neoplastic disease, drug abuse, or other relevant conditions. Medical history will be collected at screening visit only.

#### **7.1.14. Laboratory**

Blood chemistry, complete blood count with differential and platelet count will be completed at the Screening visit and at Week 12/ET<sub>12</sub>. A minimum of 8 hour fast is needed prior to blood collection for the chemistry panel. A urine drug screen will be performed at the Screening and Baseline visits (dipstick at site) and at other visits at the investigator's discretion. Pregnancy test for all women, unless surgically sterilized or at least 2 years postmenopausal will be completed at Screening and Baseline, Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12 and 16 (dipstick at site or serum).

#### **7.1.15. Cardiovascular (CV) Events of Interest**

Cardiovascular adverse events will be prospectively reviewed and adjudicated by an independent Cardiovascular Event Adjudication Committee. The committee will be blinded to study treatment allocation. The committee will confirm diagnosis for cardiovascular events of interest based on review of documentation provided by investigators. All deaths will be reviewed by the adjudication committee who will make a determination of whether a death is cardiovascular or non-cardiovascular.

Clinically significant cardiac events of interest include:

- Non-fatal myocardial infarction;
- Resuscitated cardiac arrest;
- Need for coronary revascularization;
- Hospitalization for unstable angina;
- Hospitalization for congestive heart failure;
- Fatal, non-fatal stroke or transient ischemic attack (TIA);
- Any new diagnosis of peripheral vascular disease (PVD) in a subject not previously diagnosed as having PVD or any procedure for the treatment of PVD (or any peripheral vascular intervention);
- Cardiovascular death.

In order to ensure that no potential SAEs of interest are missed, in addition to the events above any hospitalization for angina, chest pain, loss of consciousness, cardiac or vascular procedures, respiratory diseases (excluding infections and cancer), and generalized edema will be sent for adjudication as described in Section 9.8. The sponsor will periodically review adverse event lists to identify additional cases for adjudication, irrespective of the diagnosis as described in Section 9.8.

#### **7.1.15.1. Serious Cardiac Arrhythmias**

In addition to cardiac events of interest serious cardiac arrhythmias will be reviewed and adjudicated by the independent adjudication committee. Serious cardiac arrhythmias are defined as the presence of a sustained cardiac rhythm disturbance lasting more than 1 minute which results in either hemodynamic compromise, syncope, cardiac arrest, a cerebral vascular event, or altered mental status, and requires urgent intervention with cardiac monitoring, drug therapy, cardioversion, or placement of a temporary pacemaker.

Examples include:

- Ventricular tachycardia ;
- Torsade de Pointes;
- Ventricular fibrillation;
- AICD discharge (must state the underlying initiating rhythm);
- Bradycardia;

- Complete heart block;
- Atrial fibrillation / flutter;
- Supraventricular tachycardia;
- Sick sinus syndrome;
- Second degree heart block (type 2).

## **7.2. Efficacy**

### **7.2.1. Measures of Abstinence from Smoking**

Information for the calculation of abstinence parameters will be obtained at each clinic visit or telephone contact from a set of questions about cigarette and other nicotine use since the last visit/contact (Nicotine Use Inventory). At clinic visits, subject reports of smoking status will be confirmed by measurement of end expiratory exhaled carbon monoxide (CO) concentration, with a result  $\leq 10$  ppm indicating abstinence.

The main efficacy endpoint for the study is CO-confirmed 4-week continuous abstinence for Weeks 9 through 12, as determined by their answers to questions on the Nicotine Use Inventory and confirmation of their exhaled CO.

The secondary efficacy endpoint for the study is CO-confirmed continuous abstinence for Weeks 9 through 24, as determined by their answers to questions on the Nicotine Use Inventory and confirmation of their exhaled CO.

Additionally, other secondary endpoints arise from the NUI assessment:

Seven-day point prevalence of abstinence: CO-confirmed 7-day continuous abstinence for each NUI assessment visit (separately), as determined by their answers to the 'last 7 days' questions on the [Nicotine Use Inventory \(NUI\)](#) and confirmation of their exhaled CO.

## **8. ADVERSE EVENT REPORTING**

### **8.1. Adverse Events**

All observed, volunteered or solicited adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

## **8.2. Reporting Period**

For serious adverse events, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Should an investigator be made aware of any serious adverse event occurring any time after the active reporting period, it must be promptly reported.

Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject provides informed consent through last subject visit.

## **8.3. Definition of an Adverse Event**

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;

- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breast feeding;
- Medication error.

#### **8.4. Abnormal Test Findings**

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

#### **8.5. Serious Adverse Events**

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Lack of efficacy should be reported as an adverse event when it is associated with a serious adverse event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

#### **8.5.1. Potential Cases of Drug-Induced Liver Injury**

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT  $\geq 3$  times the upper limit of normal (X ULN) concurrent with a total bilirubin  $\geq 2$  X ULN with no evidence of hemolysis and an alkaline phosphatase  $\leq 2$  X ULN or not available.
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
  - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT  $\geq 2$  times the baseline values and  $\geq 3$  X ULN, or  $\geq 8$  X ULN (whichever is smaller).
  - **Concurrent with**
    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal **or**  $\geq 3$  times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct

and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting criteria a or b, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events. All study drug treatments should be discontinued in these events.

## 8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);

- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);

- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

### 8.7. Severity Assessment

If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

### 8.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section on [Reporting Requirements](#)). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.



## 8.9. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero (EIU) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product;
2. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception or is exposed during his partner's pregnancy

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to Pfizer on an EIU Form (this is a specific version of the Serious Adverse Event Form). In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the EIU Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the EIU Form that the subject was given this letter to provide to his partner.

#### **8.10. Withdrawal Due to Adverse Events (See Also Section on [Subject Withdrawal](#))**

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

#### **8.11. Eliciting Adverse Event Information**

The investigator is to report all directly observed adverse events and all adverse events voluntarily reported by the study subject. In addition, each study subject will be questioned about adverse events as described in Section 7.1.1.

#### **8.12. Reporting Requirements**

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

##### **8.12.1. Serious Adverse Event Reporting Requirements**

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breast feeding cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a

description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

#### **8.12.2. Non-Serious Adverse Event Reporting Requirements**

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

#### **8.12.3. Sponsor Reporting Requirements to Regulatory Authorities**

Adverse events reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

### **9. DATA ANALYSIS/STATISTICAL METHODS**

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

This study serves as the parent study to A3051148, the later representing an extended cardiovascular adverse event surveillance period. The endpoints for A3051123 focus on neuro-psychiatric adverse events. Hence, all other adverse events (including those cardiovascular in nature) that occur during study conduct will be reported according to Pfizer safety standards. Subsequently, all data from this parent study deemed necessary to properly summarize and report cardiovascular safety, including the derivation of composite endpoints for cardiovascular adverse events, will be incorporated into the overall evaluation of A3051148.

#### **9.1. Analysis Sets**

The Safety analysis population contains all treated subjects.

The full analysis set (FAS) is defined under the intent-to-treat principle, namely as all randomized subjects.

Treatment misallocation rules will be specified in the Statistical Analysis Plan.

## 9.2. Sample Size Determination

The study is sized to attain an adequate level of precision in the estimation of the treatment difference for varenicline and bupropion versus placebo in the incidence of the primary neuropsychiatric safety endpoint within each cohort.

For the subjects in the cohort without a diagnosis of psychiatric disorder, considering both the available data from the varenicline randomized double-blind placebo-controlled clinical trials as well as the planned usage of the NAEI to aid in data collection, the incidence estimate for placebo is assumed to be approximately 3.5% for volunteered neuropsychiatric adverse events included in the primary safety endpoint. If there were an attributable risk difference of 2.63% (which translates to a 75% increase in the relative risk scale), a sample size of 1,000 per treatment group will provide sufficient precision with an expected 95% confidence interval of (0.75% to 4.50%), ie, a margin of error of  $\pm 1.87\%$ .

For the subjects in the cohort with a diagnosis of psychiatric disorder, there are no sufficient data available and a 7.0% incidence for the placebo group is hypothesized. If there were a similar relative risk increase, an attributable risk difference of 5.25%, the sample size of 1,000 per treatment group will provide sufficient precision with an expected 95% confidence interval of (2.68% to 7.82 %), ie, a margin of error of  $\pm 2.57\%$ .

The preceding assumptions, when taken together to produce a stratified pooled estimate of risk difference, suggests that a sample size of 2,000 per treatment group will provide sufficient precision with an expected 95% confidence interval of (2.34% to 5.52%), ie, a margin of error of  $\pm 1.59\%$ .

The main abstinence (efficacy) superiority analyses are adequately powered. Given a placebo rate of 10% and 1,000 subjects per treatment group per cohort, an odds ratio of 2.0 can be detected at a 5% level with at least 80% power.

## 9.3. Safety Objective Analysis

### Primary Safety Objectives:

1. To characterize the neuropsychiatric safety profiles of varenicline and bupropion by estimating the differences from placebo with a pre-specified level of precision in the incidence of the primary neuropsychiatric AE endpoint for subjects:
  - a. With a diagnosis of psychiatric disorder;
  - b. Without a diagnosis of psychiatric disorder.
2. To characterize the differences in the neuropsychiatric safety profiles of varenicline and bupropion as compared with placebo between these sub-populations (cohorts).

Secondary safety objectives include an assessment of the above two objectives with respect to each of the remaining pairwise treatment comparisons.

The primary safety analyses will provide model-based estimates and associated 95% confidence intervals for the difference in the incidence of the primary neuropsychiatric safety endpoint between varenicline and placebo and between bupropion and placebo for subjects in each cohort. Further, an interaction involving treatment and cohort will be tested at a 10% level and, lacking evidence of significant interaction, pooled estimates of these risk differences and their associated 95% confidence intervals will be computed.

The preceding primary safety analysis will be repeated for each of the components of the composite safety endpoint.

Adverse event, laboratory, and other safety data (eg, [Hospital Anxiety and Depression Scale \(HADS\)](#) and the [Clinical Global Impression of Improvement \(CGI-I\)](#)) will be summarized by frequencies of events and or mean changes from baseline to each assessment period, as appropriate.

Additional adverse event summaries will be done for the post treatment follow up period.

The safety summaries will include:

- A summary of neuropsychiatric adverse events of interest leading to treatment and/or study discontinuations.
- A summary of neuropsychiatric adverse events of interest resulting in an intervention.

Adverse event frequencies and other safety data on the active control drug (NRT) will be summarized and tabulated.

#### **9.4. Efficacy Objective Analysis**

Main Efficacy Objective: To compare smoking abstinence rates of varenicline and bupropion relative to placebo for the last 4 weeks of treatment and continuously through Week 24, as measured by CO-confirmed CAR9-12 and CAR9-24, respectively, separately for subjects with and without a diagnosis of psychiatric disorder.

Secondary Objective: To assess if there is a difference between cohorts in the placebo adjusted relative abstinence rates (CAR9 12 and CAR9 24) of varenicline and bupropion, separately.

#### *Hypotheses and Decision Rules*

The main and secondary abstinence hypotheses are to test the superiority of varenicline versus placebo (and, separately, bupropion versus placebo), with respect to CAR9-12 and CAR9-24. Each cohort is to be tested individually at a 5% level, without any multiplicity adjustment. Furthermore, in the event that the Statistical Analysis Plan declares an interaction term(s) within the construct of a statistical model, assessment for significance of any such interaction term is to be done individually at a 10% level.

Other secondary efficacy objectives include an assessment of the above two objectives with respect to each of the remaining four pairwise treatment comparisons.

## 9.5. Methods and Analysis

The primary and secondary safety and abstinence endpoints are binary in nature. Appropriate descriptive statistics will be provided for these endpoints.

The statistical model used in the safety and abstinence analyses will be a logistic regression model that controls for the effects due to treatment, cohort and pooled site (the latter defined explicitly in the SAP).

Logistic regression analyses will be based on a binomial distribution with either an identity link function (risk difference for safety endpoints) or a logit link function (odds ratios for abstinence endpoints). Contrasts will be constructed for the primary and secondary pairwise treatment comparisons, both per cohort as well as for the pooled cohorts. For each contrast, the risk difference (or odds ratio) estimate and respective 95% confidence interval will be produced. There is no adjustment for multiplicity. Furthermore, any interaction assessment will be conducted at a 10% level. If warranted, the computation of estimates arising from the pooling of cohorts will not involve any model reduction.

Analyses for abstinence endpoints will be based on the FAS. Analyses for safety endpoints will be based on the Safety population. Adverse event data and the primary neuropsychiatric safety endpoint will be summarized and respectively analyzed using Pfizer Safety Standards and a 30-day lag following the end of 12 weeks of treatment for treatment-emergent all causality adverse events. Non-treatment-emergent adverse events (ie, from 30 days following the end of treatment through week 24) will also be summarized.

For those subjects in the “with diagnosis of psychiatric disorder” cohort, the investigator will record the primary major diagnosis group (psychotic disorders, affective disorders, anxiety disorders or borderline personality disorders) on the CRF, in effect defining a sub-cohort for each of these subjects. It is noted that with respect to analyses, cohort has two levels: (1) without diagnosis of psychiatric disorder and (2) with diagnosis of psychiatric disorder. Any secondary analysis that focuses on partitioning the “with diagnosis of psychiatric disorder” cohort will utilize the primary major diagnosis group as indicated on the CRF. Further analysis details will be presented in the SAP.

## 9.6. Interim Analysis

The unblinded primary endpoint rate (along with all AE reporting and other safety data) will be monitored at the periodic meetings of the Independent Data Monitoring Committee (IDMC). Recommendations by the IDMC to the sponsor based on the primary endpoint rate can occur throughout the study following any of the IDMC meetings. These recommendations could be related to emerging risk in one of the treatment arms or a lower primary endpoint rate than planned for in the protocol.

The sponsor will also request that the IDMC provide the blinded (pooled across both treatment and cohort) primary endpoint rate after 50% of the subjects have completed the study. If this endpoint rate is below 3.5%, then the sponsor will notify the regulators of the lower than planned endpoint rate and, if needed, request a meeting to discuss the potential implications for the study sample size and number of investigator sites.

An unblinded interim statistical analysis will be conducted and reported to the IDMC after 75% of the subjects have completed the study. This unblinded interim analysis will consist of all pair-wise treatment comparisons within and combined over the two cohorts of subjects with and without a history of psychiatric illness. Also, an upper 1-sided 95% confidence interval for the placebo primary endpoint rate in the no history cohort will be computed and projected to the planned study size. If this projected upper bound is less than 3.5%, then a sample size re-estimation will be performed. Further details will be specified within the formal Interim Analysis Plan. The sponsor will remain blinded to the interim results. The unblinded interim analysis at the 75% point is considered optimum because it will provide sufficient data (both in terms of precision and improved balance in randomization) to make recommendations regarding the possible increase in sample size as well as give sufficient time for the sponsor to implement the recommendations. Furthermore, any sample size re-estimation would apply to all treatment groups in both cohorts (ie, all treatment allocation ratios remain unchanged) and no treatment group in either cohort would stop enrollment. Any recommendations made by the IDMC as a result of the unblinded interim analysis will be communicated to the regulators before implementation.

### **9.7. Independent Data Monitoring Committee**

An Independent Data Monitoring Committee (IDMC) will be established to assess safety data at regular intervals for the duration of the trial and make recommendations to the Executive Steering Committee on whether to continue, modify or stop the study. An IDMC charter authored a priori and governed by the IDMC will be completed.

The committee will be responsible for ongoing monitoring of the safety of subjects in the study. Any recommendation made by the committee to alter the conduct of the study will be forwarded to the Sponsor for final decision. The Sponsor will forward such decisions, which may include summaries of aggregate analyses of safety endpoint events, to regulatory authorities, as appropriate.

### **9.8. Cardiovascular Event Adjudication Committee (CEAC)**

An independent adjudication committee will review documentation provided by investigators during study conduct to identify cardiovascular events of interest (primary and secondary CV safety endpoints). Investigators will collect and submit documentation to the CEAC for all adverse events related to:

- Non-fatal myocardial infarction;
- Any hospital admission for chest pain;

- Hospitalization for angina pectoris/unstable angina;
- Need for coronary revascularization or any cardiac or vascular intervention;
- Resuscitated cardiac arrest;
- Hospitalization for congestive heart failure;
- Fatal, non-fatal stroke or transient ischemic attack (TIA);
- Any diagnosis of peripheral vascular disease (PVD) in a subject not previously diagnosed as having PVD or any procedure for the treatment of PVD;
- Cardiovascular Death;
- Death from any cause:
- Hospitalization for loss of consciousness:
- Respiratory diseases (excluding infections and cancer),
- Generalized edema

To ensure that all possible cardiovascular adverse events of interest (primary and secondary endpoints) are referred to the CEAC for review, a listing of all adverse events (serious and non-serious) from the following SOC, HLGT, HLT, LLT and PTs will be prepared monthly and sent to the CEAC.

1. All Deaths.
2. SOC:
  - Cardiac Disorders;
  - General Disorders and Administration Site Conditions;
  - Injury, Poisoning, and Procedural Complications;
  - Investigations;
  - Musculoskeletal and Connective Tissue Disorders;
  - Nervous System Disorders;
  - Respiratory, Thoracic, and Mediastinal Disorders;
  - Surgical and Medical Procedures;



- Vascular Disorders.
3. HLGT:
    - Tissue disorders NEC.
  4. HLT:
    - Necrosis, NEC.
  5. LLTs:
    - Cerebral Revascularization Synangiosis (search value: revascularization);
    - Coronary Revascularization (search value: revascularization);
    - Peripheral Revascularization (search value: revascularization);
    - Renal Revascularization (search value: revascularization);
    - Transmyocardial Revascularization (search value: revascularization);
    - Acute myocardial ischemia (search value: myocardial ischemia);
    - ECG signs of myocardial ischemia (search value: myocardial ischemia);
    - Myocardial ischemia (search value: myocardial ischemia);
    - Myocardial ischemia recurrent (search value: myocardial ischemia);
    - Silent myocardial ischemia (search value: myocardial ischemia).
  6. PTs:
    - Acute Myocardial Infarction (search value: myocardial infarction);
    - Myocardial Infarction (search value: myocardial infarction);
    - Post Procedural Myocardial Infarction (search value: myocardial infarction);
    - Silent Myocardial Infarction (search value: myocardial infarction);
    - Cell Death.

These searches will be complemented by a quarterly standardized Medra query for other possible CV events that may also require adjudication.

- Myocardial Infarction;
- Ischemic Heart Disease;
- Cardiac Arrhythmias;
- Cardiac Failure;
- Embolic and Thrombotic Events;
- Shock;
- Torsade de pointes/QT prolongation;
- Cerebrovascular Disorders;
- Central Nervous System Haemorrhages and Cerebrovascular Accidents;
- Vasculitis;
- Cardiomyopathy;
- Hemodynamic edema, effusions, and fluid overload;
- Hypertension;
- Pulmonary Hypertension;
- Renovascular Disorders;
- Shock.

The events will be adjudicated using a standard events manual under blinded conditions. The adjudication committee will make the determination of whether a death is cardiac or non cardiac.

The independent adjudication committee will also review serious cardiac arrhythmias. Serious cardiac arrhythmias are defined as the presence of a sustained cardiac rhythm disturbance lasting more than 1 minute which results in either hemodynamic compromise, syncope, cardiac arrest, a cerebral vascular event, or altered mental status, and requires urgent intervention with cardiac monitoring, drug therapy, cardioversion, or placement of a temporary pacemaker.

Examples include:

- Ventricular tachycardia;

- Torsade de Pointes;
- Ventricular fibrillation;
- AICD discharge (must state the underlying initiating rhythm);
- Bradycardia;
- Complete heart block;
- Atrial fibrillation / flutter;
- Supraventricular tachycardia;
- Sick sinus syndrome;
- Second degree heart block (type 2).

## **10. QUALITY CONTROL AND QUALITY ASSURANCE**

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## **11. DATA HANDLING AND RECORD KEEPING**

### **11.1. Case Report Forms/Electronic Data Record**

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry”.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

## **11.2. Record Retention**

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## **12. ETHICS**

### **12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, Molecular Profiling Supplement, informed consent forms, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

## **12.2. Ethical Conduct of the Study**

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

## **12.3. Subject Information and Consent**

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

## **12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP**

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

### **13. DEFINITION OF END OF TRIAL**

#### **13.1. End of Trial in all Participating Countries**

End of Trial in all participating countries is defined as last subject's last visit.

### **14. SPONSOR DISCONTINUATION CRITERIA**

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of varenicline at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

### **15. PUBLICATION OF STUDY RESULTS**

#### **15.1. Communication of Results by Pfizer**

Pfizer fulfills its commitment to publicly disclose the clinical trial results through posting the results of this study on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov). Pfizer posts the results of all studies that it has registered on ClinicalTrials.gov regardless of the reason for registration.

The results are posted in a tabular format called Basic Results.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, Pfizer posts results within one year of the primary outcome completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV).
- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);
- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

## **15.2. Publications by Investigators**

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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### Appendix 1. Fagerström Test for Nicotine Dependence

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	Within 5 minutes 6-30 minutes 31-60 minutes After 60 minutes	3 2 1 0
2. Do you find it difficult to refrain from smoking in places where it is forbidden eg, in church, at the library, in the cinema, etc.?	Yes No	1 0
3. Which cigarette would you hate most to give up?	The first one in the morning Any other	1 0
4. How many cigarettes/day do you smoke?	10 or less 11-20 21-30 31 or more	0 1 2 3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes No	1 0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes No	1 0

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## **Appendix 2. Hospital Anxiety and Depression Scale (HADS)**

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and Check (✓) the reply which comes closest to how you have been feeling in the past week. Ignore the numbers printed beside each response. Don't take too long over you replies, your immediate reaction to each item will probably be more accurate than a long thought-out response.

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### Appendix 3. Suicide Behaviors Questionnaire-Revised (SBQ-R)

**Instructions:** Please check the number beside the statement or phrase that best applies to you.

**1. Have you ever thought about or attempted to kill yourself?** (check one only)

<input type="checkbox"/> 1.	Never
<input type="checkbox"/> 2.	It was just a brief passing thought
<input type="checkbox"/> 3a.	I have had a plan at least once to kill myself but did not try to do it
<input type="checkbox"/> 3b.	I have had a plan at least once to kill myself and really wanted to die
<input type="checkbox"/> 4a.	I have attempted to kill myself, but did not want to die
<input type="checkbox"/> 4b.	I have attempted to kill myself, and really hoped to die

**2. How often have you thought about killing yourself in the past year?** (check one only)

<input type="checkbox"/> 1.	Never
<input type="checkbox"/> 2.	Rarely (1 time)
<input type="checkbox"/> 3.	Sometimes (2 times)
<input type="checkbox"/> 4.	Often (3-4 times)
<input type="checkbox"/> 5.	Very Often (5 or more times)

**3. Have you ever told someone that you were going to commit suicide, or that you might do it?** (check one only)

<input type="checkbox"/> 1.	No
<input type="checkbox"/> 2a.	Yes, at one time, but did not really want to die
<input type="checkbox"/> 2b.	Yes, at one time, and really wanted to die
<input type="checkbox"/> 3a.	Yes, more than once, but did not want to do it
<input type="checkbox"/> 3b.	Yes, more than once, and really wanted to do it

**4. How likely is it that you will attempt suicide someday?** (check one only)

<input type="checkbox"/> 0.	Never	<input type="checkbox"/> 4.	Likely
<input type="checkbox"/> 1.	No chance at all	<input type="checkbox"/> 5.	Rather likely
<input type="checkbox"/> 2.	Rather unlikely	<input type="checkbox"/> 6.	Very likely
<input type="checkbox"/> 3.	Unlikely		

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#### **Appendix 4. Nicotine Use Inventory (NUI)**

##### Asked at the Baseline through the Week 12 visit

- Has the subject smoked any cigarettes (even a puff) since the last site visit / telephone contact?
- Has the subject used any other nicotine-containing products\* (e.g., nicotine patch, nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge, pipe, cigars, chew, snuff) since the last site visit / telephone contact?
- Has the subject smoked any cigarettes (even a puff) in the last 7 days?
- If the subject smoked in the last 7 days, has the subject had any days on which no cigarettes were smoked, and if so, how many days?
- If the subject smoked in the last 7 days, how many cigarettes did the subject smoke per day, on average for the days on which smoking occurred?
- Has the subject used any other nicotine-containing products\* (e.g., nicotine patch, nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge, pipe, cigars, chew, snuff) in the last 7 days?

\* This question refers to any **unauthorized** nicotine containing products and not the NRT patch which was provided during study treatment phase.

- Asked at the Week 13 visit through the Week 24 visit:
- Has the subject smoked any cigarettes (even a puff) since the last site visit / telephone contact?
- Has the subject used any other tobacco products (eg, pipe, cigars, chew, snuff) since the last site visit / telephone contact?
- Has the subject smoked any cigarettes (even a puff) in the last 7 days?
- If the subject smoked in the last 7 days, has the subject had any days on which no cigarettes were smoked, and if so, how many days?
- If the subject smoked in the last 7 days, how many cigarettes did the subject smoke per day, on average for the days on which smoking occurred?
- Has the subject used any other tobacco products (eg, pipe, cigars, chew, snuff) in the last 7 days?
- Nicotine replacement therapy and/or other smoking cessation medications should be recorded in the concomitant medicine pages in the case report form.

## Appendix 5. Aggression Questionnaire (AQ)

Instructions:

Using the 5 point scale shown below, indicate how uncharacteristic or characteristic each of the following statements is in describing you. Place your rating in the box to the right of the statement.

1 = extremely uncharacteristic of me

2 = somewhat uncharacteristic of me

3 = neither uncharacteristic nor characteristic of me

4 = somewhat characteristic of me

5 = extremely characteristic of me

1.	Some of my friends think I am a hothead
2.	If I have to resort to violence to protect my rights, I will.
3.	When people are especially nice to me, I wonder what they want.
4.	I tell my friends openly when I disagree with them.
5.	I have become so mad that I have broken things.
6.	I can't help getting into arguments when people disagree with me.
7.	I wonder why sometimes I feel so bitter about things.
8.	Once in a while, I can't control the urge to strike another person.
9.	I am an even-tempered person.
10.	I am suspicious of overly friendly strangers.
11.	I have threatened people I know.
12.	I flare up quickly but get over it quickly.
13.	Given enough provocation, I may hit another person.
14.	When people annoy me, I may tell them what I think of them.
15.	I am sometimes eaten up with jealousy.
16.	I can think of no good reason for ever hitting a person.
17.	At times I feel I have gotten a raw deal out of life.

18.	I have trouble controlling my temper.
19.	When frustrated, I let my irritation show.
20.	I sometimes feel that people are laughing at me behind my back.
21.	I often find myself disagreeing with people.
22.	If somebody hits me, I hit back.
23.	I sometimes feel like a powder keg ready to explode.
24.	Other people always seem to get the breaks.
25.	There are people who pushed me so far that we came to blows.
26.	I know that” friends” talk about me behind my back
27.	My friends say that I am somewhat argumentative
28.	Sometimes I fly off the handle for no good reason.
29.	I get into flights a little more than the average person.

## References

Buss, A.H., & Perry, M. (1992). The Aggression Questionnaire. *Journal of Personality and Social Psychology*, 63, 452-459.

## Appendix 6. Neuropsychiatric Adverse Events Interview (NAEI)

<u>Neuropsychiatric Adverse Events Interview Questions</u>	
<ul style="list-style-type: none"> <li>• Have you felt depressed (sad, blue, down, empty, as if you didn't care)?</li> <li>• Do you find that you have lost interest in things or get less pleasure from things that you used to enjoy?</li> <li>• Have you cried or felt like crying?</li> </ul>	
<ul style="list-style-type: none"> <li>• Have you been worried or scared?</li> <li>• Have you been nervous or anxious?</li> <li>• Have you felt panicky at all?</li> <li>• Some people have panic attacks when they suddenly feel very frightened and have physical symptoms like heart palpitations (your heart is pounding and/or beating rapidly), shortness of breath and chest pains. Have you had this?</li> </ul>	
<ul style="list-style-type: none"> <li>• Have you had times when you felt extremely agitated?</li> <li>• Have you had times when you felt like you had to be always moving or even pacing?</li> </ul>	
<ul style="list-style-type: none"> <li>• Have you felt unusually cheerful, or happy, not just your normal self, so that other people noticed?</li> <li>• Have you had much more energy than usual to do things?</li> <li>• Have you needed less sleep than usual to feel rested?</li> </ul>	
<ul style="list-style-type: none"> <li>• Have you felt hostile towards others?</li> <li>• Have you been involved in any serious arguments or fights?</li> <li>• Have you had the urge to injure or harm someone?</li> </ul>	
<ul style="list-style-type: none"> <li>• Have you felt that people have been talking about you?</li> <li>• Have you felt that someone may be after you, or trying to harm you in some way?</li> </ul>	
<ul style="list-style-type: none"> <li>• Has there been anything unusual about the way things look or sound or smell?</li> <li>• Have you heard things that other people couldn't hear, like noises or voices of people talking when there was no one around?</li> <li>• Have you seen things that other people couldn't see?</li> </ul>	
<ul style="list-style-type: none"> <li>• Has your mind been playing tricks on you in any way?</li> <li>• Have you had any ideas that other people might not understand or might find strange?</li> </ul>	
<ul style="list-style-type: none"> <li>• Have things seemed unreal to you?</li> <li>• Have you felt that you are detached from or have trouble connecting with other people?</li> <li>• Have you felt strange or unnatural in any other way?</li> </ul>	

## **Neuropsychiatric Adverse Events Interview (NAEI) Guidelines**

### **General Overview & Background on the NAEI**

The NAEI has been designed as a semi-structured interview to systematically assess the presence and severity of specific neuropsychiatric symptoms as part of the adverse event data collection process. The NAEI is used at Baseline to detect symptoms that are present at the time of the subject's entry into this clinical trial and at follow-up visits to prospectively monitor emergent symptoms. The goal is to facilitate the collection of information relevant to specific neuropsychiatric events of interest in a standardized manner. Standardizing the way in which such information is collected in a clinical trial optimizes reliability and validity across sites and clinicians.

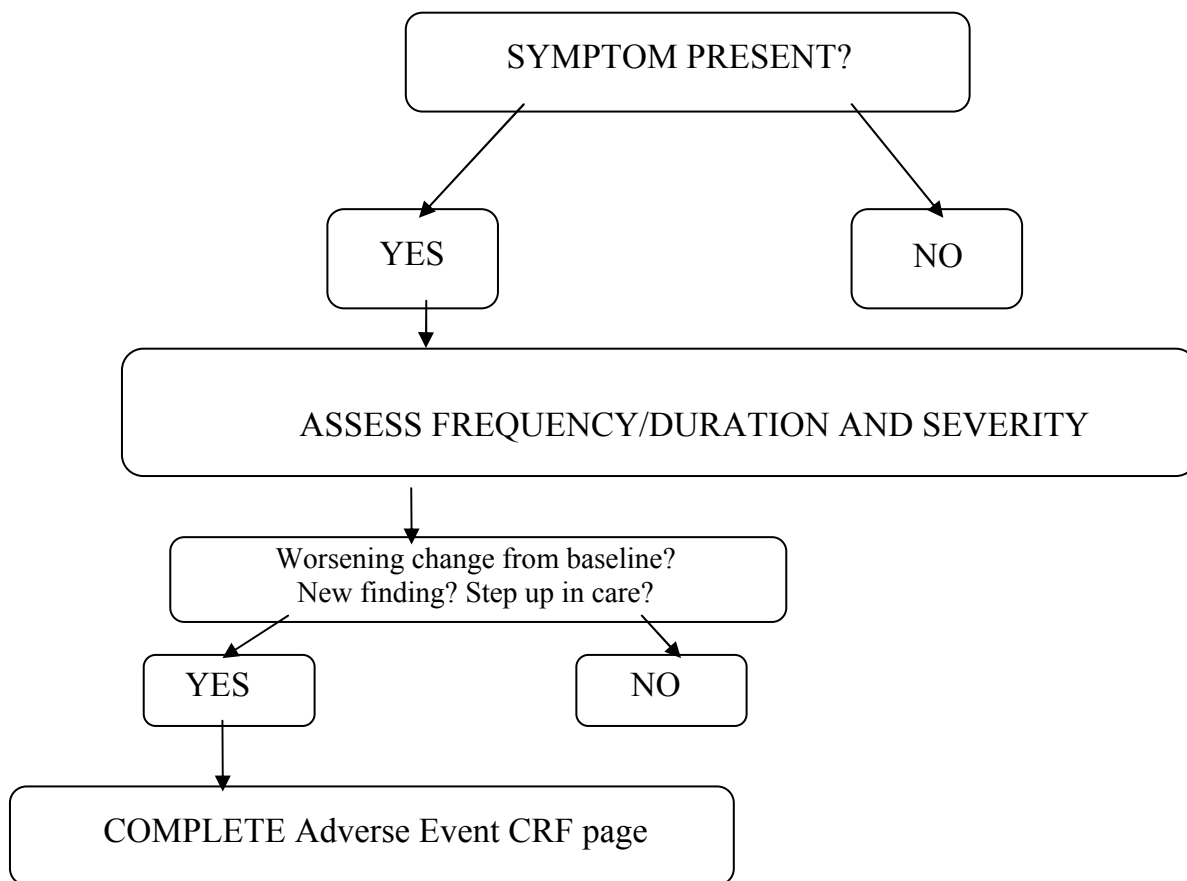
The NAEI is intended to guide the interviewer in determining whether a symptom is present, and then, if it is, clinically significant. In assessing whether a symptom's "clinical significant", it is important to examine the:

7. Frequency and duration of the symptom.
8. Severity of the symptom.

If the patient responds affirmatively to questions about a specific NAEI symptom, the symptom then must be evaluated by the investigator for clinical presentation and severity and recorded as an adverse event (AE) or serious adverse event (SAE) if warranted. AEs are graded according to their intensity (mild, moderate, or severe) by examining the degree of functional impairment associated with them as per instructions in the protocol. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. Refer to Protocol Section 8 for more information on both AE and SAE reporting.

The determination whether a symptom is an adverse event and therefore warrants an AE report should always be based on the steps outlined in the figure below:





These administration instructions are intended to help interviewers use the NAEI correctly. Sites are responsible for following these guidelines throughout the course of the study. Sites should keep a copy of these guidelines handy to refer to as needed.

A worksheet for the NAEI interview has been developed and made available to sites to facilitate its use. The worksheet is used for both the baseline and follow-up visits. The interviewer should take notes on the worksheet to assist with AE reporting if needed and to refer to during future visits.

## INTERVIEWER QUALIFICATIONS

The NAEI interview should be conducted by a staff person at the site who has completed training on the NAEI. Only interviewers who have completed the formal training on the NAEI to Pfizer's standards can administer it for this trial.

If a site needs additional training for a new interviewer, they must contact Pfizer to make arrangements for the necessary training. No interviewer should administer the NAEI without the appropriate training. Refresher training will be required during the study.

Note that where possible, sites are strongly encouraged to have the same individual conduct the volunteered AE collection, the NAEI interview, the C-SSRS, and any other clinical ratings scales included in the protocol.

Sites should make every effort to keep the same interviewer for each subject over the course of the trial.

### **Time Period to be Rated**

At Baseline, symptoms should be assessed for the past two (2) weeks. At follow-up visits, the time period to be rated is since the last clinic visit.

The interviewer should be careful when asking questions to make sure the subject is clear on the time period being rated. It may be helpful to frame questions by frequently reminding the subject of the time frame “In past 2 weeks” (at baseline) or “Since your last visit” (at follow-up) and by probing to make sure the symptoms described did occur during the time period in question (eg, at baseline asking, “Was that during the past 2 weeks?”).

### **Materials Needed to Complete the NAEI**

The NAEI guidelines should always be available for reference.

In addition, at all visits after the baseline visit, the interviewer should have at hand:

The subject’s AE log worksheet;

Previously completed NAEI worksheets.

### **Order of Assessment**

The assessment sequence for this trial must be followed carefully. Assessments should be done in the following order:

1. Volunteered AE report – opening question on how the subject has been feeling in general;
2. Follow up on previously reported AEs that are still ongoing;
3. Clinical rating scales as specified in the protocol;
4. NAEI;
5. Columbia Suicide Severity Rating Scale.

**Volunteered AE report:** The collection of volunteered AE reports should follow the site’s usual procedures. Generally this is done by asking the subject how s/he has been feeling in general. During the collection of volunteered AE information, the interviewer should be careful to ask sufficient follow-up questions to determine the clinical significance of the reported event and therefore whether an AE report is warranted.

**Follow-up of any previously reported AEs:** At all visits after the baseline visit, the interviewer then follows up on any previously reported AEs that, according to the AE log worksheet, are still ongoing (i.e., do not have a stop date) to see if resolved. AEs on the AE log worksheet may have been volunteered or solicited at previous visits.

**NAEI:** The NAEI is designed to guide the interviewer through a series of questions probing for neuropsychiatric symptoms using a semi-structured interview approach (see detailed administration instructions below). In most cases, the interviewer will need to ask all of the NAEI questions. However, some symptoms that are addressed by the NAEI questions may already have been volunteered during the volunteered AE discussion. In such situations, if the interviewer has already gained enough information to fully assess the question, it is not necessary to repeat the respective question(s) during NAEI administration.

## **BASELINE NAEI**

**TO BEGIN THE INTERVIEW:** The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had during the past two (2) weeks.

The NAEI questions have been grouped into symptom categories and all questions in each group should be asked before making a determination about a potential adverse event.

The interviewer will have to add their own follow-up questions to the written NAEI questions to obtain necessary information. Follow-up questions should be used as needed for clarification on symptoms and to assess the frequency/duration, severity, and degree of functional impairment related to the symptom. Sample follow-up questions are provided in this document. The interviewer should probe as needed to assess the subject's experiences and to make an appropriate assessment. The interviewer should be careful to clarify the time period (past 2 weeks) the questions refer to.

As noted before, once a symptom has been identified as present, its clinical significance must be ascertained.

NAEI Item Example:

During the past 2 weeks:

1. Have you been feeling sad, unhappy, worthless, or depressed?

IF YES, SAMPLE FOLLOW-UP QUESTIONS:

How often have you been bothered by this in the past 2 weeks?

Was it a little bit of the time, some of the time or most of the time?

Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people in the past 2 weeks?

IF YES: How hard? Can you give me an example?

## **FOLLOW-UP VISITS NAEI**

The purpose of this assessment is to identify symptoms that have been present since the subject's last visit and if this represents a change from their last visit. Follow-up questions are provided to help make these ratings.

To begin the follow-up interview: The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had since their last visit.

The same interview flow should be followed as at the baseline visit. In addition, for any symptom that is reported, follow up questions should assess whether this is a change from the last visit.

Follow-up NAEI Item Example:

Since your last clinic visit:

1. Have you been feeling sad, unhappy, worthless, or depressed?

Sample Follow-up Questions:

How often have you been bothered by this since your last clinic visit?

Was it a little bit of the time, some of the time or most of the time?

Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people since your last clinic visit?

IF YES: How hard? Can you give me an example?

Has this been a change from the last time you were here?

IF YES: How much of a change?

## **AFTER COMPLETING THE NAEI AT BASELINE AND FOLLOW-UP VISITS**

The interviewer should review the responses to the questions on the NAEI and notes taken during the interview, to determine whether, in his/her clinical judgment, any neuropsychiatric event reported warrants classification as an AE. Both the subject's answers to the questions and observations made during the interview should serve as the basis for making this determination.

For each solicited adverse event, the interviewer must determine the maximum level of intensity of the symptom as either:

MILD	Does not interfere with subject's usual functioning.
MODERATE	Interferes to some extent with subject's usual functioning.
SEVERE	Interferes significantly with subject's usual functioning.

AEs should be added to the subject's AE log worksheet. This, together with the completed NAEI worksheet should be filed with the subject's other documents so that they are available for future visits. The site staff should follow Pfizer's instructions to complete the AE Case Report Form page.

## Appendix 7. Clinical Global Impression of Severity (CGI-S)

**SEVERITY OF ILLNESS:** Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?

(Check (X) ONE only):		
NOT ASSESSED	NORMAL, NOT AT ALL ILL	MODERATELY ILL
	BORDERLINE, MENTALLY ILL	MARKEDLY ILL
	MILDLY ILL	SEVERELY ILL
		AMONG THE MOST EXTREMELY ILL PATIENTS

Note: The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician’s experience with the psychiatric population to which the subject belongs.

## Appendix 8. Clinical Global Impression of Improvement (CGI-I)

GLOBAL IMPRESSION OF CHANGE: Rate total impression of change whether or not, in your judgment, it is due entirely to drug treatment.

Compared to his/her condition at the Week 0 Visit, how much has the patient changed?

(Check (X) ONE only):		
NOT ASSESSED	VERY MUCH IMPROVED	NO CHANGE
	MUCH IMPROVED	MINIMALLY WORSE
	MINIMALLY IMPROVED	MUCH WORSE
		VERY MUCH WORSE

Note: The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). For those subjects with a psychiatric diagnosis, the clinician should rate the severity of the mental illness with respect to the clinician’s experience with the psychiatric population to which the subject belongs.

## Appendix 9. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) Baseline

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;  
Burke, A.; Oquendo, M.; Mann, J.*

### Disclaimer:

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact [posnerk@childpsych.columbia.edu](mailto:posnerk@childpsych.columbia.edu)  
© 2008 The Research Foundation for Mental Hygiene, Inc.*



<b>SUICIDAL IDEATION</b>		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.		Lifetime: Time He/She Felt Most Suicidal
<b>1. Wish to be Dead</b> Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>2. Non-Specific Active Suicidal Thoughts</b> General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan. <i>Have you actually had any thoughts of killing yourself?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b> Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <i>Have you been thinking about how you might do this?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b> Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>5. Active Suicidal Ideation with Specific Plan and Intent</b> Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i>  If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/>	
<b>INTENSITY OF IDEATION</b>		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.		Most Severe
<b>Most Severe Ideation:</b> _____ <div style="display: flex; justify-content: space-around;"> <span>Type # (1-5)</span> <span>Description of Ideation</span> </div>		
<b>Frequency</b> <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		_____
<b>Duration</b> <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time		_____
<b>Controllability</b> <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (6) Does not attempt to control thoughts		_____
<b>Deterrents</b> <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (6) Does not apply		_____
<b>Reasons for Ideation</b> <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (6) Does not apply		_____

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## Appendix 10. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) Since Last Visit

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.;  
Burke, A.; Oquendo, M.; Mann, J.*

### Disclaimer:

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact [posnerk@childpsych.columbia.edu](mailto:posnerk@childpsych.columbia.edu)*

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<b>SUICIDAL IDEATION</b>		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.		Since Last Visit
<b>1. Wish to be Dead</b> Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>2. Non-Specific Active Suicidal Thoughts</b> General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b> Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it." <i>Have you been thinking about how you might do this?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b> Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>5. Active Suicidal Ideation with Specific Plan and Intent</b> Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i>  If yes, describe:		Yes No <input type="checkbox"/> <input type="checkbox"/>
<b>INTENSITY OF IDEATION</b>		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).		
Most Severe Ideation: _____ <div style="display: flex; justify-content: space-around;"> <span>Type # (1-5)</span> <span>Description of Ideation</span> </div>		Most Severe
<b>Frequency</b> <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		_____
<b>Duration</b> <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time		_____
<b>Controllability</b> <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (6) Does not attempt to control thoughts		_____
<b>Deterrents</b> <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (6) Does not apply		_____
<b>Reasons for Ideation</b> <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (6) Does not apply		_____

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## Appendix 11. List of Abbreviations

AE	adverse event
AHRQ	Agency Healthcare Research and Quality
ANOVA	Analysis of Variance
ARISg	Global Adverse Reaction Information System
AQ	Aggression Questionnaire
BID	twice daily
BMI	body mass index
BP	blood pressure
CAR	continuous abstinence rate
C-CASA	Columbia Classification Algorithm of Suicide Assessment
C-SSRS	Columbia Suicide Severity Rating Scale
CO	carbon monoxide
CQR	continuous quit rate
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression- Severity
CRF	case report form
DSMC	Data Safety Monitoring Committee
DSM-IV TR	Diagnostic and Statistic Manual of Mental Disorders 4 <sup>th</sup> Edition Text Revision
ECG	electrocardiogram
ET	early termination
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent to treat
MHP	mental health professional (psychiatrist or licensed PhD level clinical psychologist)
mm	millimeter
mmHg	millimeters of mercury
NAEI	Neuropsychiatric Adverse Event Interview
NUI	Nicotine Use Inventory
PDS	Pfizer Data Standards
ppm	parts per million
PR	pulse rate
QD	once daily
SAE	serious adverse event
SBQ-R	Suicide Behaviors Questionnaire-Revised
SCID	Structured Clinical Interview for DSM Disorders
TQD	target quit day
ULN	upper limit of normal

## **Appendix 12. CV Required Documents**

Deaths and cardiovascular events of interest will be reviewed and adjudicated by an independent events committee. The committee will review all pertinent information for each reported case.

Clinical sites will forward all the available records with the appropriate routing form for adjudication.

### **Any Hospitalization for loss of consciousness, cardiac or vascular procedures, respiratory diseases (excluding infections and cancer) and generalized edema:**

- Admission notes;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Laboratory imaging and ancillary examinations.

### **Hospitalization for Chest Pain or Angina Pectoris/Unstable angina:**

- Admission notes;
- Discharge summary;
- ECG tracing(s) (include eRT ECG);
- Stress test or Thallium scan;
- Angiography report;
- Summary of Event in English (signed by an MD);
- Other (for example, MUGA scan, Holter);
- Cardiac enzymes:
  - CK;
  - CK-MB;
  - LDH;
  - Troponin I;
  - Troponin T;

**Hospitalization for Congestive Heart Failure:**

- Admission notes;
- Physician notes/progress reports supporting typical CHF symptoms and signs or other diagnostic test results;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Chest x-ray;
- ECG tracings;
- Ejections fraction by echocardiogram, MUGA scans, etc.;
- Brain natriuretic peptide (BNP) and NT-proBNP results should be submitted, if available;
- Other.

**Coronary Revascularization Procedure (CABG, PTCA, Atherectomy, Transplant, Other)**

- Admission notes;
- Physician notes/progress reports;
- Operative report;
- Catheterization report;
- PTCA operative reports;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Other.

**Non-fatal Myocardial Infarction or Resuscitated Cardiac Arrest**

- Discharge Summary;
- Clinical Notes;
- Summary of Event in English (signed by an MD);



- Cardiac imaging data (if available);
- ECG tracing(s) (include eRT ECG);
- Cardiac enzymes:
  - CK;
  - CK-MB;
  - LDH Troponin I;
  - Troponin I;
  - Other.

#### **Non-fatal Stroke, TIA**

- Admission and/or physician progress notes, including neurological exam;
- Discharge summary;
- Summary of Event in English (signed by MD);
- Operative Report;
- CT;
- MRI;
- Angiography Report;
- Spinal Fluid Analysis;
- Other.

#### **First Diagnosis of PVD or Procedure for PVD**

- Physician Notes;
- Summary of Event in English (signed by an MD);
- Diagnostic Tests (angiograms, Dopplers, etc.);
- PVD procedure;
- Percutaneous Revascularization (ie, atherectomy, PTA);

- Amputation;
- Other.

### **Serious Cardiac Arrhythmias**

- Physician Notes;
- Summary of Event in English (signed by an MD);
- Diagnostic Tests;
- Admission notes if applicable;
- Discharge summary;
- ECG tracing(s) (include eRT ECG);
- Other (for example, Holter).

### **Deaths**

- Physician Notes;
- Summary of Event in English (signed by an MD);
- Admission and/or physician progress notes;
- Diagnostic tests if applicable;
- Discharge summary if applicable;
- Autopsy Report (if performed);
- Other.

## Appendix 13. CLINICAL PROTOCOL AMENDMENT 1

Current Amendment: 1

Amendment No.	Date	Country (ies)	Site(s)
1	17 June 2010		

Previous Amendments:

Amendment No.	Date	Country (ies)	Site(s)
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### SUMMARY

#### Reason(s) for Amendment

The protocol is being amended to incorporate changes requested by the US FDA (Agency), to clarify certain protocol aspects and to correct inconsistencies/ typographical errors. The changes requested by FDA were to use a different guidance for suicide risk, clarifying that primary focus of suicide risk assessment is the presence or absence of current significant suicidality. The Agency asked that the following wording was added to the protocol: training and background requirements for administering the SCID; narratives for all moderate events included in the composite primary endpoint; instructions to record all AEs irrespective of the mechanism for ascertainment in the AE CRF; description of AE collection using the NAEI, including guidelines to the investigator in the appendix; instructions in the appendices and text to instruct investigators that CGI-S and CGI-I ratings are in reference to psychiatric diagnoses; revision to the additional inclusion criteria for the neuropsychiatric cohort to specify that both a current condition and a lifetime diagnosis are eligible for inclusion; reference to the pilot study to test the NAEI; and correction on schedule of activities to include C-SSRS assessment at Week 10. Minor corrections for inconsistencies were performed as detailed below.

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

#### Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

The “change from” section represents the current text in the protocol. Bolded text is used to indicate the addition of information to the current text, and strike-out of text (eg, ~~text~~) is used to show the deletion of information from the current text.

The “change to” section represents the revised text, with the revisions shown in the “change from” section in normal text.

Section <Insert section number> , <Insert section title> , Page  
<Insert page number as appropriate>

#### Change From

#### Change To

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# **1. Section, SCHEDULE OF ACTIVITIES - Study Treatment period and Post Treatment Period**

## **Change From**

## **SCHEDULE OF ACTIVITIES- Study Treatment Period**

Procedure	Screen	BL	Wk 1 (Day 8)	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7*	Wk 8	Wk 9*	Wk 10	Wk 11*	Wk 12	ET <sup>a</sup> 12
Informed Consent <sup>b</sup>	X														
Medical History, Demography, Smoking history/ height	X														
Physical Examination	X														
Vital Signs (HR, BP)	X	X												X	X
Weight	X	X												X	X
SCID I and II	X														
Adverse Events Volunteered reporting (NAEI)		X	X	X	X	X	X	X		X		X		X	X
Concomitant Medications and Non-Drug Treatment	X	X	X	X	X	X	X	X		X		X		X	X
CGI-S	X	X													
CGI-I			X	X	X	X	X	X		X		X		X	X
HADS		X	X	X	X	X	X	X		X		X		X	X
Aggression Questionnaire		X													
Neuropsychiatric Adverse Event Interview (NAEI)		X	X	X	X	X	X	X		X		X		X	X
SBQ-R	X														
C-SSRS	X	X	X	X	X	X	X	X		X		X		X	X
NUI		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fagerström Test	X														
Exhaled CO	X	X	X	X	X	X	X	X		X		X		X	X
Dispense Study Drugs		X	X	X	X	X	X	X		X		X			
EKG	X														
CBC, Blood Chemistry	X													X	X
Pregnancy Test <sup>c</sup> (urine or serum)	X	X													
Urine Drug Screen <sup>d</sup> (dipstick at site)	X	X													
Emergency Contact Information Card		X													
Counseling (≤10 minutes)		X	X	X	X	X	X	X		X		X		X	X

### SCHEDULE OF ACTIVITIES- Post - Treatment Period

Procedure	Wk 13	Wk 14*	Wk 15*	Wk 16	Wk 17*	Wk 18*	W 19*	Wk 20	Wk 21*	Wk 22*	Wk 23*	Wk 24	ET <sup>a</sup> 24
<b>Weight</b>												<b>X</b>	<b>X</b>
Adverse Events Volunteered reporting	X			X				X				X	X
CGI-I	X			X				X				X	X
HADS	X			X				X				X	X
Neuropsychiatric Adverse Event Interview	X			X				X				X	X
C-SSRS	X			X				X				X	X
NUI	X	X	X	X	X	X	X	X	X	X	X	X	X
Exhaled CO	X			X				X				X	X
Concomitant Medications and Non-Drug Treatment	X			X				X				X	X
Counseling (≤10 minutes)	X			X				X				X	X

### Change To

### SCHEDULE OF ACTIVITIES- Study Treatment Period

Procedure	Screen	BL	Wk 1 (Day 8)	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7*	Wk 8	Wk 9*	Wk 10	Wk 11*	Wk 12	ET <sup>a</sup> 12
Informed Consent <sup>b</sup>	X														
Medical History, Demography, Smoking history/ height	X														
Physical Examination	X														
Vital Signs (HR, BP)	X	X												X	X
Weight		X												X	X
SCID I and II	X														
Adverse Events Volunteered reporting		X	X	X	X	X	X	X		X		X		X	X
Concomitant Medications and Non-Drug Treatment	X	X	X	X	X	X	X	X		X		X		X	X
CGI-S	X	X													
CGI-I			X	X	X	X	X	X		X		X		X	X
HADS		X	X	X	X	X	X	X		X		X		X	X
Aggression Questionnaire		X													
Neuropsychiatric Adverse Event Interview (NAEI)		X	X	X	X	X	X	X		X		X		X	X
SBQ-R	X														
C-SSRS	X	X	X	X	X	X	X	X		X		X		X	X
NUI		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fagerström Test	X														
Exhaled CO	X	X	X	X	X	X	X	X		X		X		X	X
Dispense Study Drugs		X	X	X	X	X	X	X		X		X			

Procedure	Screen	BL	Wk 1 (Day 8)	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7*	Wk 8	Wk 9*	Wk 10	Wk 11*	Wk 12	ET <sup>a</sup> 12
EKG	X														
CBC, Blood Chemistry	X													X	X
Pregnancy Test <sup>c</sup> (urine or serum)	X	X													
Urine Drug Screen <sup>d</sup> (dipstick at site)	X	X													
Emergency Contact Information Card		X													
Counseling (≤10 minutes)		X	X	X	X	X	X	X		X		X		X	X

## SCHEDULE OF ACTIVITIES- Post - Treatment Period

Procedure	Wk 13	Wk 14*	Wk 15*	Wk 16	Wk 17*	Wk 18*	Wk 19*	Wk 20	Wk 21*	Wk 22*	Wk 23*	Wk 24	ET <sup>a</sup> 24
Weight												X	X
Adverse Events Volunteered reporting	X			X				X				X	X
CGI-I	X			X				X				X	X
HADS	X			X				X				X	X
Neuropsychiatric Adverse Event Interview	X			X				X				X	X
C-SSRS	X			X				X				X	X
NUI	X	X	X	X	X	X	X	X	X	X	X	X	X
Exhaled CO	X			X				X				X	X
Concomitant Medications and Non-Drug Treatment	X			X				X				X	X
Counseling (≤10 minutes)	X			X				X				X	X

## 2. Section 4. SUBJECT SELECTION, 4.1. Inclusion Criteria, 5<sup>th</sup> bullet

### Change From

- A **double** barrier method of contraception, eg, condom and/or diaphragm with spermicide while participating in the study through at least 30 days after the last dose of study medication or abstinence.

### Change To

- A double barrier method of contraception, eg, condom and diaphragm with spermicide while participating in the study through at least 30 days after the last dose of study medication or abstinence.

**3. Section 4. SUBJECT SELECTION, 4.1.1. Additional Inclusion Criteria for Neuropsychiatric Cohort, 2<sup>nd</sup> paragraph and 2 footnotes**

**Change From**

All subjects will be screened for Axis I and II diagnosis (current and/or past) using DSM IV TR criteria based on clinical assessment and confirmed by SCID (**administered by a clinician or trained mental health professional, ie; a PhD level clinical psychologist, or an individual with master level training in related areas [masters level psychologist, social work] who have been trained to use the SCID**). Subjects will be included in the psychiatric cohort, if they are considered clinically stable by the Investigator and ~~currently~~ meet criteria, **either current or lifetime diagnosis**, for one or more of the DSM-IV diagnoses listed below and have met diagnostic criteria before the initiation of study treatment. If the Investigator is not a psychiatrist or licensed PhD level clinical psychologist, he/she should consult with a mental health professional (MHP) to determine if the subject is stable.

<sup>1</sup>Clinician is defined as someone licensed to practice medicine according to existing regulations

<sup>2</sup>Documentation of training will be kept at the clinical site.

**Change To**

All subjects will be screened for Axis I and II diagnosis (current and/or past) using DSM IV TR criteria based on clinical assessment and confirmed by SCID (administered by a clinician or trained mental health professional, ie; a PhD level clinical psychologist, or an individual with master level training in related areas [masters level psychologist, social work] who have been trained to use the SCID). Subjects will be included in the psychiatric cohort, if they are considered clinically stable by the Investigator and meet criteria, either current or lifetime diagnosis, for one or more of the DSM-IV diagnoses listed below and have met diagnostic criteria before the initiation of study treatment. If the Investigator is not a psychiatrist or licensed PhD level clinical psychologist, he/she should consult with a mental health professional (MHP) to determine if the subject is stable.

<sup>1</sup>Clinician is defined as someone licensed to practice medicine according to existing regulations

<sup>2</sup>Documentation of training will be kept at the clinical site.

**4. Section 4. SUBJECT SELECTION, 4.2 Exclusion Criteria, 3<sup>rd</sup> paragraph, number 3, 4<sup>th</sup> - 7<sup>th</sup> bullets**

**Change From**

If the subjects **described above (exclusionary co-morbid psychiatric condition)** do not meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, they are not eligible for the study. **Subjects who meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, and who have a co-morbid condition not listed in the protocol (for example, agoraphobia without history of panic attacks) may be eligible for inclusion in the psychiatric arm if in the opinion of the investigator the concurrent**

**condition is stable and does not prevent the subject from safely complying with study procedures. In such cases, please consult with the medical monitor.**

3. Subjects who are believed to have a suicidal risk at screening, baseline, or after assessment by a qualified mental health professional (Psychiatrist or licensed PhD level clinical psychologist) if a risk assessment interview was required after screening or baseline using the ~~Suicidal Behaviors Questionnaire Revised (SBQ-R) Appendix 3 and~~ Columbia Suicide Severity Rating Scale (C-SSRS). Appendix 9:

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on items 4, 5 ~~or any suicidal behavioral questions of the C-SSRS.~~ Appendix 9.
- Previous history of suicide behaviors in the past ~~10~~ years,
- ~~Any lifetime history of serious or recurrent suicidal behavior,~~
- ~~SBQ-R total score  $\geq 8$ .~~

#### **Change To**

If the subjects described above (exclusionary co-morbid psychiatric condition) do not meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, they are not eligible for the study. Subjects who meet a primary diagnosis listed in Inclusion Criteria of the psychiatric arm, and who have a co-morbid condition not listed in the protocol (for example, agoraphobia without history of panic attacks) may be eligible for inclusion in the psychiatric arm if in the opinion of the investigator the concurrent condition is stable and does not prevent the subject from safely complying with study procedures. In such cases, please consult with the medical monitor.

3. Subjects who are believed to have a suicidal risk at screening, baseline, or after assessment by a qualified mental health professional (Psychiatrist or licensed PhD level clinical psychologist) if a risk assessment interview was required after screening or baseline using the Columbia Suicide Severity Rating Scale (C-SSRS). Appendix 9:

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS. Appendix 9.
- Previous history of suicide behaviors in the past year,

#### **5. Section 6. STUDY PROCEDURES, 6.1. Screening, 4<sup>th</sup> and 19<sup>th</sup> bullets**

#### **Change From**

- Measure and record height ~~and weight~~;
- Psychiatric evaluation if warranted (See Section 7.1.10 ~~7.1.7~~).



#### Change To

- Measure and record height;
- Psychiatric evaluation if warranted (See Section 7.1.10).

#### 6. Section 6. STUDY PROCEDURES, 6.2.1. Baseline Visit (Randomization), 1<sup>st</sup> and 18<sup>th</sup> bullets

#### Change From

- Record sitting blood pressure, ~~and~~ pulse rate **and weight**;
- Psychiatric evaluation if warranted (See Section 7.1.10 ~~7.1.7~~).

#### Change To

- Record sitting blood pressure, pulse rate and weight;
- Psychiatric evaluation if warranted (See Section 7.1.10).

#### 7. Section 6. STUDY PROCEDURES, 6.3.1. Clinic Visits (Weeks 13, 16, 20, 24 and ET<sub>24</sub> Visit), 1<sup>st</sup> bullet

#### Addition

**Record Body Weight (Week 24 and ET<sub>24</sub> only);**

#### 8. Section 7. ASSESSMENTS, 7.1.1. Adverse Events, 1<sup>st</sup>, 2<sup>nd</sup> and 4<sup>th</sup> paragraphs

#### Change From

All adverse events (AEs) ~~volunteered, spontaneously observed, or solicited (of all severities) or reported~~ will be recorded **in the AE CRF** up to and including Week 24.

~~In addition, actively solicited~~ Solicited neuropsychiatric adverse events will be collected by use of the Neuropsychiatric Adverse Event Interview (NAEI) at each clinic visit (starting from baseline) up to and including Week 24. The voluntarily reported AEs will be assessed first at each study visit followed by the NAEI and then the C-SSRS.

Suicide related adverse events will be solicited by completion of the C-SSRS at each clinic visit up to and including Week 24. Any severe neuropsychiatric adverse event(s) **or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide)** recorded will require the subject to be referred for a psychiatric evaluation by a qualified mental health professional MHP (Psychiatrist or licensed PhD level clinical psychologist) (Section 7.1.10 ~~7.1.9~~) and a narrative will be

constructed for each ~~severe~~ event. In the event the investigator meets the requirements of the MHP, he/she may complete this evaluation.

#### **Change To**

All adverse events (AEs) volunteered, observed, or solicited (of all severities) will be recorded in the AE CRF up to and including Week 24.

Solicited neuropsychiatric adverse events will be collected by use of the Neuropsychiatric Adverse Event Interview (NAEI) at each clinic visit (starting from baseline) up to and including Week 24. The voluntarily reported AEs will be assessed first at each study visit followed by the NAEI and then the C-SSRS.

Suicide related adverse events will be solicited by completion of the C-SSRS at each clinic visit up to and including Week 24. Any severe neuropsychiatric adverse event(s) or moderate adverse events of interest (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide) recorded will require the subject to be referred for a psychiatric evaluation by a qualified mental health professional MHP (Psychiatrist or licensed PhD level clinical psychologist) (Section 7.1.10) and a narrative will be constructed for each event. In the event the investigator meets the requirements of the MHP, he/she may complete this evaluation.

#### **9. Section 7. ASSESSMENTS, 7.1.1.1. Primary Neuropsychiatric Safety Endpoint, 5<sup>th</sup> and 7<sup>th</sup> paragraphs**

#### **Change From**

**Items captured from proxy report (ie, PCP, family member) judged to be adverse events by the Investigator;**

The primary safety endpoint encompasses events reported (**via the AE CRF page**) through any of the above ~~three~~ means of assessments. Additionally, the MedDRA version and Preferred Terms to be included in the primary safety endpoint will be described in the Statistical Analysis Plan.

#### **Change To**

Items captured from proxy report (ie, PCP, family member) judged to be adverse events by the Investigator;

The primary safety endpoint encompasses events reported (via the AE CRF page) through any of the above means of assessments. Additionally, the MedDRA version and Preferred Terms to be included in the primary safety endpoint will be described in the Statistical Analysis Plan.

**10. Section 7. ASSESSMENTS, 7.1.1.2. Actively Solicited Neuropsychiatric Adverse Events**

**Change From**

The Neuropsychiatric Adverse Event Interview (NAEI) Appendix 6, will actively inquire about the following type of adverse events: aggression, anxiety, agitation, depression, delusions, dissociative states, feeling abnormal, hallucinations, homicidal ideation, hostility, mania, paranoia, panic, and psychosis. If a subject has a positive response to any item on the NAEI, a determination will be made by the investigator as to whether this meets criteria for an adverse event. If it does meet criteria as an adverse event it will be recorded on the adverse event pages of the Case Report Form. **A pilot study is being conducted to test the NAEI in a similar population to the one to be included in this study (patients with and without a history of psychiatric disease enrolled in a smoking cessation program).**

**Change To**

The Neuropsychiatric Adverse Event Interview (NAEI) Appendix 6, will actively inquire about the following type of adverse events: aggression, anxiety, agitation, depression, delusions, dissociative states, feeling abnormal, hallucinations, homicidal ideation, hostility, mania, paranoia, panic, and psychosis. If a subject has a positive response to any item on the NAEI, a determination will be made by the investigator as to whether this meets criteria for an adverse event. If it does meet criteria as an adverse event it will be recorded on the adverse event pages of the Case Report Form. A pilot study is being conducted to test the NAEI in a similar population to the one to be included in this study (patients with and without a history of psychiatric disease enrolled in a smoking cessation program).

**11. Section 7. ASSESSMENTS, 7.1.2. Columbia Suicide Severity Rating Scale (C-SSRS) Appendix 9, Appendix 10 and the Suicidal Behaviors Questionnaire (SBQ-R) Appendix 3, 1st- 3<sup>rd</sup> bullets**

**Change From**

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on items 4, 5 ~~or any suicidal behavioral questions~~ of the C-SSRS; Appendix 9;
- Previous history of suicide behaviors in the past ~~10~~ years;
- ~~Any lifetime history of serious or recurrent suicidal behavior;~~
- ~~SBQ-R total score  $\geq 8$ ;~~

**Change To**

- Suicide ideation associated with actual intent and/or plan in the past year: Yes answers on item 5 of the C-SSRS; Appendix 9;

- Previous history of suicide behaviors in the past year;

## 12. Section 7. ASSESSMENTS, 7.1.4. Clinical Global Impression of Severity (CGI-S) Appendix 7

### Change From

The CGI-S is a clinician rated instrument measuring the severity of a subject's psychiatric condition on a 7 point scale at time of assessment, relative to clinician's past experience in patients with same diagnosis. The scores are: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; or 7=extremely ill. **The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as "Normal, not at all ill" on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as "No change" on the CGI-I at follow up visits).** This scale should be administered by the same rater throughout the study whenever possible.

### Change To

The CGI-S is a clinician rated instrument measuring the severity of a subject's psychiatric condition on a 7 point scale at time of assessment, relative to clinician's past experience in patients with same diagnosis. The scores are: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; or 7=extremely ill. The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as "Normal, not at all ill" on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as "No change" on the CGI-I at follow up visits). This scale should be administered by the same rater throughout the study whenever possible.

## 13. Section 7. ASSESSMENTS, 7.1.5. Clinical Global Impression of Improvement (CGI-I) Appendix 8

### Change From

The CGI-I is a clinician rated instrument that measures change in subject's psychiatric condition (or lack thereof in the stratum without psychiatric disorders) on a 7 point scale ranging from 1 (very much improved) to 7 (very much worse). **The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as "Normal, not at all ill" on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as "No change" on the CGI-I at follow up visits).** This scale should be administered by the same rater throughout the study whenever possible.

### Change To

The CGI-I is a clinician rated instrument that measures change in subject's psychiatric condition (or lack thereof in the stratum without psychiatric disorders) on a 7 point scale

ranging from 1 (very much improved) to 7 (very much worse). The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits). This scale should be administered by the same rater throughout the study whenever possible.

**14. Section 7. ASSESSMENTS, 7.1.10. Psychiatric Evaluations/Risk Assessments, 2<sup>nd</sup>, - 4<sup>th</sup> bullets**

**Change From**

- Subject answers “yes” on items 4, 5 ~~or on any suicidal behavioral question on~~ C-SSRS during the screening visit or **subject answers “yes” on item 4, 5 or on any suicidal behavioral question on C-SSRS during the study;**
- Previous history of suicide behaviors in the past ~~10~~ years (prior to randomization);
- ~~Any lifetime history of serious or recurrent suicidal behavior (prior to randomization);~~
- ~~SBQ-R total score  $\geq 8$  at screening.~~

**Change To**

- Subject answers “yes” on item 5, on C-SSRS during the screening visit or subject answers “yes” on item 4, 5 or on any suicidal behavioral question on C-SSRS during the study;
- Previous history of suicide behaviors in the past year (prior to randomization);

**15. Section 7. ASSESSMENTS, 7.1.12. Physical Examination, Vital Signs and Electrocardiogram, 3<sup>rd</sup> paragraph**

**Change From**

Sitting blood pressure and pulse **rate** will be measured at the screening and baseline visits and Wk 12 or ET<sub>12</sub>. Blood pressure will be measured by an appropriate automated/semi-automated or manual sphygmomanometer and recorded to the nearest mmHg. All blood pressure measurements are to be taken in the dominant arm with the appropriate size cuff. Pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

**Change To**

Sitting blood pressure and pulse rate will be measured at the screening and baseline visits and Wk 12 or ET<sub>12</sub>. Blood pressure will be measured by an appropriate automated/semi-automated or manual sphygmomanometer and recorded to the nearest

mmHg. All blood pressure measurements are to be taken in the dominant arm with the appropriate size cuff. Pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

**16. Section 9. DATA ANALYSIS/STATISTICAL METHODS, 9.3. Safety Objectives Analysis, 7<sup>th</sup> paragraph and last 2 bullets**

**Addition**

The safety summaries will also be expanded to specifically include:

- A summary of neuropsychiatric adverse events of interest leading to treatment and/or study discontinuations.
- A summary of neuropsychiatric adverse events of interest resulting in an intervention.

**17. Section 9. DATA ANALYSIS/STATISTICAL METHODS, 9.5. Methods and Analysis, last paragraph**

**Addition**

The investigator will record the primary major diagnosis group (the sub-stratification of the psychiatric disorder cohort) in the CRF. S and secondary analyses involving this primary major diagnosis group will utilize this classification be completed. Further analysis details will be presented in the SAP.

**18. Section, APPENDICES, Appendix 5. Aggression Questionnaire (AQ), title**

**Change From**

Appendix 5. Aggression Questionnaire (AQ)<sup>+</sup>

**Change To**

Appendix 5. Aggression Questionnaire (AQ)

**19. Section, APPENDICES, Appendix 6. Neuropsychiatric Adverse Events Interview (NAEI), after 1<sup>st</sup> page**

**Addition**

**General Overview & Background on the NAEI**

The NAEI has been designed as a semi-structured interview to systematically assess the presence and severity of specific neuropsychiatric symptoms as part of the adverse event data collection process. The NAEI is used at Baseline to detect symptoms that are present at the time of the subject's entry into this clinical trial and at follow-up visits to

**prospectively monitor emergent symptoms. The goal is to facilitate the collection of information relevant to specific neuropsychiatric events of interest in a standardized manner. Standardizing the way in which such information is collected in a clinical trial optimizes reliability and validity across sites and clinicians.**

**The NAEI is intended to guide the interviewer in determining whether a symptom is present, and then, if it is, clinical significance. In assessing whether a symptom's "clinical significant", it is important to examine the**

**(1) frequency and duration of the symptom.**

**(2) severity of the symptom**

**If the patient responds affirmatively to questions about a specific NAEI symptom, the symptom then must be evaluated by the investigator for clinical presentation and severity and recorded as an adverse event (AE) or serious adverse event (SAE) if warranted. AEs are graded according to their intensity (mild, moderate, or severe) by examining the degree of functional impairment associated with them as per instructions in the protocol. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. Refer to Protocol Section 8 for more information on both AE and SAE reporting.**

**The determination whether a symptom is an adverse event and therefore warrants an AE report should always be based on the steps outlined in the figure below:**

**These administration instructions are intended to help interviewers use the NAEI correctly. Sites are responsible for following these guidelines throughout the course of the study. Sites should keep a copy of these guidelines handy to refer to as needed.**

**A worksheet for the NAEI interview has been developed and made available to sites to facilitate its use. The worksheet is used for both the baseline and follow-up visits. The interviewer should take notes on the worksheet to assist with AE reporting if needed and to refer to during future visits.**

## **INTERVIEWER QUALIFICATIONS**

**The NAEI interview should be conducted by a staff person at the site who has completed training on the NAEI. Only interviewers who have completed the formal training on the NAEI to Pfizer's standards can administer it for this trial.**

**If a site needs additional training for a new interviewer, they must contact Pfizer to make arrangements for the necessary training. No interviewer should administer the NAEI without the appropriate training. Refresher training will be required during the study.**

**Note that where possible, sites are strongly encouraged to have the same individual conduct the volunteered AE collection, the NAEI interview, the C-SSRS, and any other clinical ratings scales included in the protocol.**

**Sites should make every effort to keep the same interviewer for each subject over the course of the trial.**

#### **Time Period to be Rated**

**At Baseline, symptoms should be assessed for the past two (2) weeks. At follow-up visits, the time period to be rated is since the last clinic visit.**

**The interviewer should be careful when asking questions to make sure the subject is clear on the time period being rated. It may be helpful to frame questions by frequently reminding the subject of the time frame “In past 2 weeks” (at baseline) or “Since your last visit” (at follow-up) and by probing to make sure the symptoms described did occur during the time period in question (e.g., at baseline asking, “Was that during the past 2 weeks?”).**

#### **Materials Needed to Complete the NAEI**

**The NAEI guidelines should always be available for reference.**

**In addition, at all visits after the baseline visit, the interviewer should have at hand**

- the subject’s AE log worksheet**
- previously completed NAEI worksheets**

#### **Order of Assessment**

**The assessment sequence for this trial must be followed carefully. Assessments should be done in the following order:**

- 6. Volunteered AE report – opening question on how the subject has been feeling in general**
- 7. Follow up on previously reported AEs that are still ongoing**
- 8. Clinical rating scales as specified in the protocol**
- 9. NAEI**



## **10. Columbia Suicide Severity Rating Scale**

**Volunteered AE report:** The collection of volunteered AE reports should follow the site's usual procedures. Generally this is done by asking the subject how s/he has been feeling in general. During the collection of volunteered AE information, the interviewer should be careful to ask sufficient follow-up questions to determine the clinical significance of the reported event and therefore whether an AE report is warranted.

**Follow-up of any previously reported AEs:** At all visits after the baseline visit, the interviewer then follows up on any previously reported AEs that, according to the AE log worksheet, are still ongoing (i.e., do not have a stop date) to see if resolved. AEs on the AE log worksheet may have been volunteered or solicited at previous visits.

**NAEI:** The NAEI is designed to guide the interviewer through a series of questions probing for neuropsychiatric symptoms using a semi-structured interview approach (see detailed administration instructions below). In most cases, the interviewer will need to ask all of the NAEI questions. However, some symptoms that are addressed by the NAEI questions may already have been volunteered during the volunteered AE discussion. In such situations, if the interviewer has already gained enough information to fully assess the question, it is not necessary to repeat the respective question(s) during NAEI administration.

### **BASELINE NAEI**

**TO BEGIN THE INTERVIEW:** The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had during the past two (2) weeks.

The NAEI questions have been grouped into symptom clusters and all questions in each group should be asked before making a determination about a potential adverse event.

The interviewer will have to add their own follow-up questions to the written NAEI questions to obtain necessary information. Follow-up questions should be used as needed for clarification on symptoms and to assess the frequency/duration, severity, and degree of functional impairment related to the symptom. Sample follow-up questions are provided in this document. The interviewer should probe as needed to assess the subject's experiences and to make an appropriate assessment. The interviewer should be careful to clarify the time period (past 2 weeks) the questions refer to.

As noted before, once a symptom has been identified as present, its clinical significance must be ascertained.

### **NAEI Item Example:**

**During the past 2 weeks:**

**1. Have you been feeling sad, unhappy, worthless, or depressed?**

**IF YES, SAMPLE FOLLOW-UP QUESTIONS:**

- **How often have you been bothered by this in the past 2 weeks?**

**Was it a little bit of the time, some of the time or most of the time?**

**Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people in the past 2 weeks?**

**IF YES: How hard? Can you give me an example?**

**FOLLOW-UP VISITS NAEI**

**The purpose of this assessment is to identify symptoms that have been present since the subject's last visit and if this represents a change from their last visit. Follow-up questions are provided to help make these ratings.**

**To begin the follow-up interview: The interviewer should explain that the interview will focus on problems or difficulties that the subject may have had since their last visit.**

**The same interview flow should be followed as at the baseline visit. In addition, for any symptom that is reported, follow up questions should assess whether this is a change from the last visit.**

**Follow-up NAEI Item Example:**

**Since your last clinic visit:**

**1. Have you been feeling sad, unhappy, worthless, or depressed?**

**Sample Follow-up Questions:**

**How often have you been bothered by this since your last clinic visit?**

**Was it a little bit of the time, some of the time or most of the time?**

**Has [this symptom] made it hard for you to do your work, take care of things at home, or get along with other people since your last clinic visit?**

**IF YES: How hard? Can you give me an example?**

**Has this been a change from the last time you were here?**

**IF YES: How much of a change?**

**AFTER COMPLETING THE NAEI AT BASELINE AND FOLLOW-UP VISITS**

**The interviewer should review the responses to the questions on the NAEI and notes taken during the interview, to determine whether, in his/her clinical judgment, any neuropsychiatric event reported warrants classification as an AE. Both the subject's answers to the questions and observations made during the interview should serve as the basis for making this determination.**

**For each solicited adverse event, the interviewer must determine the maximum level of intensity of the symptom as either:**

MILD	Does not interfere with subject's usual functioning.
MODERATE	Interferes to some extent with subject's usual functioning.
SEVERE	Interferes significantly with subject's usual functioning.

**AEs should be added to the subject's AE log worksheet. This, together with the completed NAEI worksheet should be filed with the subject's other documents so that they are available for future visits. The site staff should follow Pfizer's instructions to complete the AE Case Report Form page.**

**20. Section, APPENDICES, Appendix 7. Global Clinical Impression of Severity (CGI-S), last paragraph**

**Addition**

**Note: The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as "Normal, not at all ill" on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as "No change" on the CGI-I at follow up visits).**

**21. Section, APPENDICES, Appendix 8. Global Clinical Impression of Improvement (CGI-I), table and last paragraph**

**Change From**

(Check (X) ONE only):		
NOT ASSESSED	VERY MUCH IMPROVED	NO CHANGE
	MUCH IMPROVED	MINIMALLY WORSE
	MINIMALLY IMPROVED	MUCH WORSE
		VERY MUCH WORSE

(Check (X) ONE only):		
NOT ASSESSED	NORMAL, NOT AT ALL ILL	MODERATELY ILL
	BORDERLINE, MENTALLY ILL	MARKEDLY ILL
	MILDLY ILL	SEVERELY ILL
		AMONG THE MOST EXTREMELY ILL PATIENTS

**Note:** The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits).

**Change To**

(Check (X) ONE only):		
NOT ASSESSED	VERY MUCH IMPROVED	NO CHANGE
	MUCH IMPROVED	MINIMALLY WORSE
	MINIMALLY IMPROVED	MUCH WORSE
		VERY MUCH WORSE

**Note:** The ratings will be applicable even to those without psychiatric diagnoses (eg, those with no psychiatric symptoms would be rated as “Normal, not at all ill” on the CGI-S at baseline.) and assuming no psychiatric symptoms emerge during the trial, would be rated as “No change” on the CGI-I at follow up visits).

**22. Section, APPENDICES, Appendix 9. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS), (Baseline), 1<sup>st</sup> page after Disclaimer**

**Deletion**

(Check (X) ONE only):		
NOT ASSESSED	VERY MUCH IMPROVED	NO CHANGE
	MUCH IMPROVED	MINIMALLY WORSE
	MINIMALLY IMPROVED	MUCH WORSE
		VERY MUCH WORSE

**23. Section, APPENDICES, Appendix 10. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) (Since Last Visit)**

**Change From**

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer: This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of Suicidality depends on clinical judgement.

SUICIDAL IDEATION		<del>Lifetime— Time He/She Felt Most Suicidal Since Last Visit</del>
Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes,” ask questions 3, 4 and 5.		
1. Wish To Be Dead		
Have you wished you were dead or wished you could go to sleep and not wake up?		Yes/No
Frequency of ideation _____		
If yes, describe.		
2. Non-Specific Active Suicidal Thoughts		
Have you actually had any thoughts of killing yourself? Frequency of ideation _____		Yes/No
If yes, describe.		
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act		
Have you been thinking about how you might do this? Frequency of ideation _____		Yes/No
If yes, describe.		

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Have you had these thoughts and had some intention of acting on them? Frequency of ideation \_\_\_\_\_ Yes/No

If yes, describe.

5. Active Suicidal Ideation with Specific Plan and Intent

Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan? Frequency of ideation \_\_\_\_\_ Yes/No

If yes, describe.

**INTENSITY OF IDEATION**

The following features should be rated with respect to both most common and most severe types of ideation. Ask about time he/she was feeling the most suicidal. Only rate most common if most severe and most common are different.

**Since Last Visit**  
**Time He/She Felt Most Suicidal**  
**Lifetime**  
**Time He/She Felt Most Suicidal**

Ideation Type

Type # (1-5)

Description of

Ideation

Most

Common

Most

Severe

Baseline

Most Common Ideation: \_\_\_\_\_

Most Severe Ideation: \_\_\_\_\_

**Frequency**

How many times have you had these thoughts?

1. Less than once a week
2. Once a week
3. 2-5 times in week
4. Daily or almost daily
5. Many times each day

\_\_\_\_\_

\_\_\_\_\_

**Duration**

When you have the thoughts how long do they last?

1. Fleeting – few seconds or minutes
2. Less than 1 hour/some of the time
3. 1-4 hours/a lot of time
4. 4-8 hours/most of day
5. More than 8 hours/persistent or continuous

\_\_\_\_\_

\_\_\_\_\_

**Controllability**

Could/can you stop thinking about killing yourself or wanting to die if you want to?

1. Easily able to control thoughts
2. Can control thoughts with little difficulty
3. Can control thoughts with some difficulty
4. Can control thoughts with a lot of difficulty
5. Unable to control thoughts
0. Does not attempt to control thoughts

\_\_\_\_\_

\_\_\_\_\_

**Deterrents**

Are there things – anyone or anything (eg family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?

1. Deterrents definitely stopped you from attempting suicide
2. Deterrents probably stopped you
3. Uncertain that deterrents stopped you
4. Deterrents most likely did not stop you
0. Does not apply, wish to die only

\_\_\_\_\_

\_\_\_\_\_

#### Reasons for Ideation

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?

1. Completely to get attention, revenge or a reaction from others \_\_\_\_\_
2. Mostly to get attention, revenge or a reaction from others \_\_\_\_\_
3. Equally to get attention , revenge or a reaction from others and to end/stop the pain \_\_\_\_\_
4. Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). \_\_\_\_\_
5. Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). \_\_\_\_\_

#### SUICIDAL BEHAVIOR

(Check all that apply, so long as these are separate events; must ask about all types)

Since Last  
Visit ~~Lifetime~~  
Time He/She  
Felt Most  
Suicidal

##### Actual Attempt:

Have you made a suicide attempt? Yes/No

Have you done anything to harm yourself?

Have you done anything dangerous where you could have died?

What did you do?

Did you \_\_\_\_\_ as a way to end your life?

Did you want to die (even a little) when you \_\_\_\_\_?

Were you trying to end your life when you \_\_\_\_\_?

Or did you think it was possible you could have died from \_\_\_\_\_?

Total # of  
attempts \_\_\_\_\_

Or did you do it purely for other reasons / without any intention of killing your self (like to relieve stress, feel better, get sympathy, or to get something else to happen)? (*Self-injurious behavior without suicidal intent*)

If yes, describe.

Yes/No

##### Has the subject engaged in Non-Suicidal Self-Injurious Behavior?

##### Interrupted Attempt:

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? Yes/No

If yes, describe.

Total # of  
interrupted \_\_\_\_\_

##### Aborted Attempt:

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? Yes/No

If yes, describe.

Total # of  
aborted \_\_\_\_\_

##### Preparatory Acts or Behavior:

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? Yes/No

If yes, describe.

Suicidal Behavior:

Suicidal behavior was present during the assessment period? Yes/No

If yes, describe.

Completed Suicide: Yes/No

ANSWER FOR ACTUAL ATTEMPTS ONLY	Most Recent Attempt Date:	Worst/Most Lethal Attempt Date:	Since Last Visit Initial/First Attempt Date:
Actual Lethality/Medical Damage:	Enter Code	Enter Code	Enter Code
0. No physical damage or very minor physical damage (eg, surface scratches).			
1. Minor physical damage (eg, lethargic speech; first-degree burns; mild bleeding; sprains).			
2. Moderate physical damage; medical attention needed (eg, conscious but sleepy, somewhat responsive; second degree burns; bleeding of major vessel).			
3. Moderately severe physical damage; medical hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).	_____	_____	_____
4. Severe physical damage; medical hospitalization with intensive care required (eg, comatose without reflexes; third degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).			
5. Death			
Potential Lethality: Only Answer if Actual Lethality = 0	Enter Code	Enter Code	Enter Code
0 = Behavior not likely to result in injury			
1 = Behavior likely to result in injury but not likely to cause death			
2 = Behavior likely to result in death despite available medical care			

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032. (Oquendo M. A.; Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M. B. First [Ed.] *Standardized Evaluation in Clinical Practice*, pp. 103 – 130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact [posnerk@childpsych.columbia.edu](mailto:posnerk@childpsych.columbia.edu).

### Change To

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer: This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of Suicidality depends on clinical judgement.



SUICIDAL IDEATION		Since Last Visit
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5.		
<b>1. Wish To Be Dead</b>		
Have you wished you were dead or wished you could go to sleep and not wake up?		Yes/No
Frequency of ideation _____		
If yes, describe.		
<b>2. Non-Specific Active Suicidal Thoughts</b>		
Have you actually had any thoughts of killing yourself? Frequency of ideation _____		Yes/No
If yes, describe.		
<b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b>		
Have you been thinking about how you might do this? Frequency of ideation _____		Yes/No
If yes, describe.		
<b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b>		
Have you had these thoughts and had some intention of acting on them? Frequency of ideation _____		Yes/No
If yes, describe.		
<b>5. Active Suicidal Ideation with Specific Plan and Intent</b>		
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan? Frequency of ideation _____		Yes/No
If yes, describe.		

INTENSITY OF IDEATION		Since Last Visit	
The following features should be rated with respect to both most common and most severe types of ideation. Ask about time he/she was feeling the most suicidal. Only rate most common if most severe and most common are different.			
Ideation Type	Type # (1-5)	Description of	
Ideation		Most Common	Most Severe
<b>Baseline</b>			
Most Common Ideation: _____			
Most Severe Ideation: _____			
<b>Frequency</b>			
How many times have you had these thoughts?			
1. Less than once a week			
2. Once a week			
3. 2-5 times in week			
4. Daily or almost daily			
5. Many times each day			
<b>Duration</b>			
When you have the thoughts how long do they last?			
1. Fleeting – few seconds or minutes			
2. Less than 1 hour/some of the time			
3. 1-4 hours/a lot of time			
4. 4-8 hours/most of day			
5. More than 8 hours/persistent or continuous			
<b>Controllability</b>			
Could/can you stop thinking about killing yourself or wanting to die if you want to?			
1. Easily able to control thoughts			
2. Can control thoughts with little difficulty			
3. Can control thoughts with some difficulty			
4. Can control thoughts with a lot of difficulty			

5. Unable to control thoughts  
 0. Does not attempt to control thoughts

**Deterrents**

Are there things – anyone or anything (eg family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?

1. Deterrents definitely stopped you from attempting suicide  
 2. Deterrents probably stopped you  
 3. Uncertain that deterrents stopped you  
 4. Deterrents most likely did not stop you  
 0. Does not apply, wish to die only

**Reasons for Ideation**

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?

1. Completely to get attention, revenge or a reaction from others  
 2. Mostly to get attention, revenge or a reaction from others  
 3. Equally to get attention, revenge or a reaction from others and to end/stop the pain  
 4. Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).  
 5. Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).

SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)	Since Last Visit
<b>Actual Attempt:</b>	
Have you made a suicide attempt?	Yes/No
Have you done anything to harm yourself?	
Have you done anything dangerous where you could have died?	
What did you do?	Total # of attempts _____
Did you _____ as a way to end your life?	
Did you want to die (even a little) when you _____?	
Were you trying to end your life when you _____?	
Or did you think it was possible you could have died from _____?	
Or did you do it purely for other reasons / without any intention of killing your self (like to relieve stress, feel better, get sympathy, or to get something else to happen)? ( <i>Self-injurious behavior without suicidal intent</i> )	
If yes, describe.	Yes/No
Has the subject engaged in Non-Suicidal Self-Injurious Behavior?	
<b>Interrupted Attempt:</b>	
Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?	Yes/No
If yes, describe.	Total # of interrupted _____
<b>Aborted Attempt:</b>	
Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?	Yes/No
If yes, describe.	Total # of aborted _____
<b>Preparatory Acts or Behavior:</b>	
Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?	Yes/No

If yes, describe.

**Suicidal Behavior:**

Suicidal behavior was present during the assessment period?

Yes/No

If yes, describe.

**Completed Suicide:**

Yes/No

ANSWER FOR ACTUAL ATTEMPTS ONLY	Most Recent Attempt Date:	Worst/Most Lethal Attempt Date:	Since Last Visit:
<b>Actual Lethality/Medical Damage:</b>	<b>Enter Code</b>	<b>Enter Code</b>	<b>Enter Code</b>
0. No physical damage or very minor physical damage (eg, surface scratches).			
1. Minor physical damage (eg, lethargic speech; first-degree burns; mild bleeding; sprains).			
2. Moderate physical damage; medical attention needed (eg, conscious but sleepy, somewhat responsive; second degree burns; bleeding of major vessel).			
3. Moderately severe physical damage; medical hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).			
4. Severe physical damage; medical hospitalization with intensive care required (eg, comatose without reflexes; third degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).			
5. Death			
<b>Potential Lethality: Only Answer if Actual Lethality = 0</b>	<b>Enter Code</b>	<b>Enter Code</b>	<b>Enter Code</b>
0 = Behavior not likely to result in injury			
1 = Behavior likely to result in injury but not likely to cause death			
2 = Behavior likely to result in death despite available medical care			

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032. (Oquendo M. A.; Halberstam B. & Mann J. J., Risk factors for suicidal bahvior: utility and limitations of research instruments. In M. B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 – 130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu.

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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Drug Utilization Review**

Date: September 03, 2014

Reviewer: Rajdeep Gill Pharm.D.,  
Drug Utilization Data Analysis Acting Team Leader  
Division of Epidemiology II (DEPI II)

Acting Deputy Director: Hina Mehta, Pharm.D.,  
Acting Deputy Director for Drug Utilization  
Division of Epidemiology II (DEPI II)

Division Director: Judy Staffa, Ph.D., RPh.  
Division of Epidemiology II (DEPI II)

Drug Name(s): Chantix<sup>®</sup> (varenicline) tablets

Application Type/Number: 21928

Applicant/Sponsor: Pfizer

OSE RCM #: 2014-749

**\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\***

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## EXECUTIVE SUMMARY

To assist the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) prepare for an upcoming advisory committee meeting to discuss Chantix<sup>®</sup> (varenicline) and risk for neuropsychiatric events, this review analyzes the drug utilization patterns for Chantix<sup>®</sup> (varenicline) and comparator agents.

The overall sales of various smoking cessation products; prescription (Rx) and over-the-counter (OTC) products, decreased by approximately 36% from approximately 9.5 million bottles/packages sold in 2009 to 6.1 million bottles/packages sold in 2013. During 2013, prescription products accounted for approximately 52% (3.1 million bottles/packages) and OTC products accounted for approximately 48% (2.9 million bottles/packages) of the total sales of smoking cessation products.

Among prescription smoking cessation products, a vast majority of utilization was for Chantix<sup>®</sup> (varenicline). The number of prescriptions dispensed for Chantix<sup>®</sup> (varenicline) increased from approximately 30 prescriptions dispensed during the 2<sup>nd</sup> quarter of 2006 (approval in May 2006) to a peak of approximately 2 million prescriptions dispensed in the 4<sup>th</sup> quarter of 2007 and then eventually decreased to approximately 531,000 prescriptions dispensed in the 1<sup>st</sup> quarter of 2014. The number of patients receiving dispensed prescriptions for Chantix<sup>®</sup> (varenicline) decreased from approximately 3.9 million patients in 2007 to approximately 1.2 million patients in 2013. Patients aged 45-64 years accounted for majority of the patients receiving a dispensed prescription for Chantix<sup>®</sup> (varenicline). Females accounted for approximately 53-56% and males accounted for approximately 44-47% of the total patients receiving a dispensed prescription for Chantix<sup>®</sup> (varenicline) during the time period examined. Utilization of Zyban<sup>®</sup> (brand and generic), Nicotrol<sup>®</sup> inhaler and Nicotrol<sup>®</sup> nasal spray decreased over time.

The overall number of packages of OTC nicotine replacement products sold through retail settings fluctuated during the time examined with approximately 1.7 million packages sold in the 4<sup>th</sup> quarter of 2013. Among the OTC nicotine replacement products, the gum formulation accounted for the highest proportion of the total retail sales followed by lozenges and patches.

## 1 INTRODUCTION

### 1.1 BACKGROUND

The Division of Analgesia, Anesthesia and Addiction Products (DAAAP) is currently preparing for a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting to be held on October 16, 2014 to discuss the risk of serious neuropsychiatric adverse events with Chantix<sup>®</sup> (varenicline) tablets (NDA 21928) and to further discuss options for addressing this risk.<sup>1</sup>

In preparation for the advisory committee meeting, the Division of Epidemiology II was requested to provide the drug utilization patterns for Chantix<sup>®</sup> (varenicline) as well as Zyban<sup>®</sup> (brand and generic), Nicotrol<sup>®</sup> inhaler, Nicotrol<sup>®</sup> nasal spray and over-the-counter (OTC) nicotine replacement products (patches, gum and lozenges).

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<sup>1</sup> <http://www.fda.gov/advisorycommittees/calendar/ucm394876.htm>; accessed August 2014

## 1.2 PRODUCT LABELING

Chantix<sup>®</sup> (varenicline) is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment and was approved in May 2006.<sup>2</sup>

Chantix<sup>®</sup> (varenicline) is available as 0.5 mg and 1mg oral tablets.

## 2 METHODS AND MATERIALS

### 2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspective<sup>™</sup> was used to determine the various retail and non-retail channels of distribution for Chantix<sup>®</sup> (varenicline). Sales data for 2013 indicated that approximately 90% of Chantix<sup>®</sup> (varenicline) was distributed to the outpatient retail pharmacy setting while the mail-order/specialty pharmacy and the non-retail pharmacy settings accounted for 7% and 3.5% of the total sales, respectively<sup>3</sup>. As a result, only the outpatient retail pharmacy utilization patterns were examined in this review. Retail pharmacies include chain stores, independent pharmacies, and food store pharmacies. Non-retail pharmacy and mail-order/specialty pharmacy settings data were not included in this analysis.

### 2.2 DATA SOURCES USED

Proprietary drug utilization databases were used to conduct this analysis (see Appendix 2 for full database description).

The IMS Health, National Sales Perspectives<sup>™</sup> database was used to provide the nationally estimated number of bottles/packages of prescription (Rx) smoking cessation products and over-the-counter (OTC) nicotine replacement products sold from manufacturers to retail and non-retail channels of distribution in the U.S. from 2009 through 2013, yearly. These sales data represent the amount of product being sold from manufacturers into the “back door” of various drug distribution outlets such as retail pharmacies, hospitals, clinics, etc.; it does not reflect what is being sold to or administered to patients directly.

The IMS Health, National Prescription Audit (NPA) was used to obtain the nationally estimated number of prescriptions dispensed for Chantix<sup>®</sup> (varenicline) as well as Zyban<sup>®</sup> (brand and generic), Nicotrol<sup>®</sup> inhaler, and Nicotrol<sup>®</sup> nasal spray through U.S. outpatient retail pharmacies from approval May 2006 through March 2014, quarterly.

The IMS Health, Total Patient Tracker (TPT) was used to obtain the nationally estimated number of patients who received a dispensed prescription Chantix<sup>®</sup> (varenicline) as well as Zyban<sup>®</sup> (brand and generic), Nicotrol<sup>®</sup> inhaler, and Nicotrol<sup>®</sup> nasal spray from U.S. outpatient retail pharmacies for years 2006 through 2013. The IMS Health, Total Patient Tracker (TPT) was also used to obtain nationally estimated number of patients who received a dispensed prescription Chantix<sup>®</sup> (varenicline) stratified by patient age (0-17, 18-24, 25-44, 45-64, 65 years and older) and sex for years 2006 through 2013.

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<sup>2</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/021928s030lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021928s030lbl.pdf); label accessed August 2014

<sup>3</sup> IMS Health, National Sales Perspectives (NSP), Data extracted August 2014. File: NSPC 2017-749 chantix channels 08-04-14.xlsx



The OTC International Market Tracking (OTCIMS) database was used to provide the nationally estimated number of packages of OTC nicotine replacement products sold, stratified by formulation, from various U.S. outpatient retail store outlets to the consumers from 2009 through 2013, quarterly. Although these sales data show the amount of product being sold through the front end, direct patient use of the over-the-counter products is not captured as information of the actual or intended user is not captured.

### 3 RESULTS

#### 3.1 SALES DATA

**Figure 1 in Appendix 1** provides the nationally estimated number of bottles/packages of Rx smoking cessation products and OTC nicotine replacement products sold from manufacturers to retail and non-retail channels of distribution in the U.S. for 2009 through 2013. The overall sales of various smoking cessation products, both Rx and OTC, decreased by approximately 36% from 9.5 million bottles/packages sold in 2009 to 6.1 million bottles/packages sold in 2013. In 2009, Rx products accounted for approximately 47% (4.4 million bottles/packages) and OTC products accounted for approximately 53% (5.1 million bottles/packages) of the total sales of smoking cessations products. In 2013, Rx products accounted for approximately 52% (3.1 million bottles/packages) and OTC products accounted for approximately 48% (2.9 million bottles/packages) of the total sales of smoking cessations products.

#### 3.2 PRESCRIPTION DATA

**Figure 2 in Appendix 1** provides the nationally estimated number of dispensed prescriptions for Chantix<sup>®</sup> (varenicline) as well as Zyban<sup>®</sup> (brand and generic), Nicotrol<sup>®</sup> inhaler, and Nicotrol<sup>®</sup> nasal spray from U.S. outpatient retail pharmacies from the 2<sup>nd</sup> quarter of 2006 through the 1<sup>st</sup> quarter of 2014. The number of prescriptions dispensed for Chantix<sup>®</sup> (varenicline) increased from approximately 30 prescriptions dispensed during the 2<sup>nd</sup> quarter of 2006 to a peak of approximately 2 million prescriptions dispensed in the 4<sup>th</sup> quarter of 2007 and then eventually decreased to approximately 531,000 prescriptions dispensed in the 1<sup>st</sup> quarter of 2014. In the 1<sup>st</sup> quarter of 2014 approximately 28,000 Zyban<sup>®</sup> (brand and generic) prescriptions were dispensed while 16,000 and 5,600 prescriptions of Nicotrol<sup>®</sup> inhaler and Nicotrol<sup>®</sup> nasal spray were dispensed, respectively. In comparison to Chantix much fewer prescriptions were dispensed for Zyban<sup>®</sup> (brand and generic), Nicotrol<sup>®</sup> inhaler and Nicotrol<sup>®</sup> nasal spray during the entire time period examined.

#### 3.3 PATIENT DATA

**Figure 3 in Appendix 1** provides the nationally estimated number of unique patients who received a dispensed prescription for Chantix<sup>®</sup> (varenicline) as well as Zyban<sup>®</sup> (brand and generic), Nicotrol<sup>®</sup> inhaler, and Nicotrol<sup>®</sup> nasal spray from U.S. outpatient retail pharmacies from 2006 through 2013. Patient data were similar to prescription data. The number of unique patients receiving a prescription for Chantix<sup>®</sup> (varenicline) increased from approximately 573,000 patients in 2006 to a peak of approximately 3.9 million patients in 2007 and then decreased to approximately 1.15 million patients in 2013 accounting for a 70% decrease. In comparison to Chantix, many fewer patients received dispensed prescriptions for Zyban<sup>®</sup> (brand and generic), Nicotrol<sup>®</sup> inhaler and Nicotrol<sup>®</sup> nasal spray during each year examined. During 2013, approximately 49,000 patients received a dispensed prescription for Zyban<sup>®</sup> (brand and generic) while approximately 51,000



patients and 7,000 patients received a dispensed prescription for Nicotrol<sup>®</sup> inhaler and Nicotrol<sup>®</sup> nasal spray, respectively.

### 3.4 CHANTIX: PATIENT DATA BY AGE AND SEX

**Table 1 in Appendix 1** provides the nationally estimated number of unique patients (stratified by sex and age) who received a dispensed prescription Chantix<sup>®</sup> (varenicline) from U.S. outpatient retail pharmacies from 2006 through 2013. Patients aged 45-64 years accounted for the greatest proportion of the total patients receiving a dispensed prescription for Chantix<sup>®</sup> (varenicline) with approximately 49% of the total or 569,000 patients, followed by patients aged 25-44 years with approximately 39% or 446,000 patients during 2013. Patients aged 65 years and above accounted for approximately 9% of the total or 106,000 patients and patients aged 18-24 years accounted for approximately 3% or 35,000 patients. During the time examined, the proportion of patients aged 45-64 years receiving a dispensed prescription for Chantix<sup>®</sup> (varenicline) decreased and the proportion of patients aged 25-44 years receiving a dispensed prescription increased.

Females accounted for approximately 53-56% of the total patients and males accounted for approximately 44-47% of the total patients receiving a dispensed prescription for Chantix<sup>®</sup> (varenicline) during the time period examined. During the time examined, the proportion of female patients aged 45-64 years receiving a dispensed prescription for Chantix<sup>®</sup> (varenicline) decreased while the proportion of female patients aged 25-44 years receiving a dispensed prescription increased. Similar patterns were seen for male patients.

### 3.5 OTC DATA

**Figure 4 in Appendix 1** provides the number of packages of OTC nicotine replacement products, stratified by product formulation, sold from U.S. outpatient retail store outlets (point of sale) to consumers from the 1<sup>st</sup> quarter of 2009 to the 4<sup>th</sup> quarter of 2013. The overall number of packages of OTC nicotine replacement products sold fluctuated during the time examined with approximately 1.7 million packages sold in the 4<sup>th</sup> quarter of 2013. Throughout the examined time period, the gum formulation accounted for the highest proportion of the total retail sales. The number of packages of the gum formulation increased from approximately 811,000 packages (46% of the total retail sales) sold in the 1<sup>st</sup> quarter of 2009 to approximately 1.1 million packages (57% of the total retail sales) sold in the 4<sup>th</sup> quarter of 2013. During the same time period, the number of packages of the lozenge formulation decreased slightly from approximately 380,000 packages (26% of total retail sales) sold in the 1<sup>st</sup> quarter of 2009 to approximately 327,000 packages (25% of the total retail sales) sold in the 4<sup>th</sup> quarter of 2013. Meanwhile, the number of packages of the patch formulation decreased from approximately 402,000 packages (28% of total retail sales) sold in the 1<sup>st</sup> quarter of 2009 to approximately 251,000 packages (19% of the total retail sales) sold in the 4<sup>th</sup> quarter of 2013.

## 4 DISCUSSION

The overall findings from this review illustrate that the sales of smoking cessation products (Rx and OTC) decreased over the time period examined. The vast majority of use was for Chantix<sup>®</sup> (varenicline) among the prescription smoking cessation products. *Of note, we only included products that are labelled for smoking cessation in our analysis. We did not include products that may be used off-label, such as Wellbutrin (Bupropion) SR and XL and the generic equivalents.*

The OTC sales data illustrated that the number of packages of over-the-counter nicotine replacement products fluctuated over the time period examined, with the gum formulation accounting for the largest proportion of the total OTC sales.

Findings from this review should be interpreted in the context of the known limitations of the databases used. The IMS Health, IMS National Sales Perspectives™, sales data for 2013 indicated that the majority of (90% of total sales) Chantix® (varenicline) was distributed to the outpatient retail pharmacy setting. These data do not provide a direct estimate of use, they represent the amount of product being sold from manufacturers into the “back door” of various drug distribution outlets (e.g. retail pharmacies, hospitals, clinics, etc.) – it does not reflect what is being sold to or administered to patients directly.

For the prescription smoking cessation products, we focused our analysis on only the outpatient retail pharmacy settings, therefore these estimates may not apply to other settings of care, such as mail-order/specialty pharmacies, clinics, and hospitals, in which these products are used.

The OTCIMS database tracks retail sales data and captures approximately 70% of sales activity of over-the-counter products from retail drug stores, food stores, and mass merchandisers (excluding Wal-Mart) – retail sales data are projected to represent U.S. retailer universe. We focused our OTC analyses on only the outpatient retail settings, therefore these estimates may not apply to other settings of care such as on-line purchasing. Due to these limitations, not all of the retail sales or the household purchasing data of OTC nicotine replacement products in the U.S. is captured in this analysis, and the true extent of use of OTC nicotine replacement products is at best underestimated. Moreover, direct patient use is not available as information of the actual or intended user is not captured. As a result, a reliable estimate of direct patient use of OTC products is not possible.

All the estimates provided in this analysis (sales data, prescription data, patient data, and OTC data) are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

## **5 CONCLUSION**

The overall sales of prescription and over-the-counter smoking cessation products decreased over the time period examined. During 2013, prescription products accounted for approximately 52% (3.1 million bottles/packages) and OTC products accounted for approximately 48% (2.9 million bottles/packages) of the total sales of smoking cessation products. Among prescription products, the majority of utilization was for Chantix® (varenicline). The number of patients receiving a dispensed prescription for Chantix® (varenicline) decreased from approximately 3.9 million patients in 2007 to approximately 1.2 million patients in 2013. Utilization of Zyban® (brand and generic), Nicotrol® inhaler and Nicotrol® nasal spray also decreased over time. Among the over-the-counter nicotine replacement products, the gum formulation accounted for the highest proportion of the total retail sales followed by lozenges and patches.

## APPENDIX 1: Tables and Figures.

Figure 1.

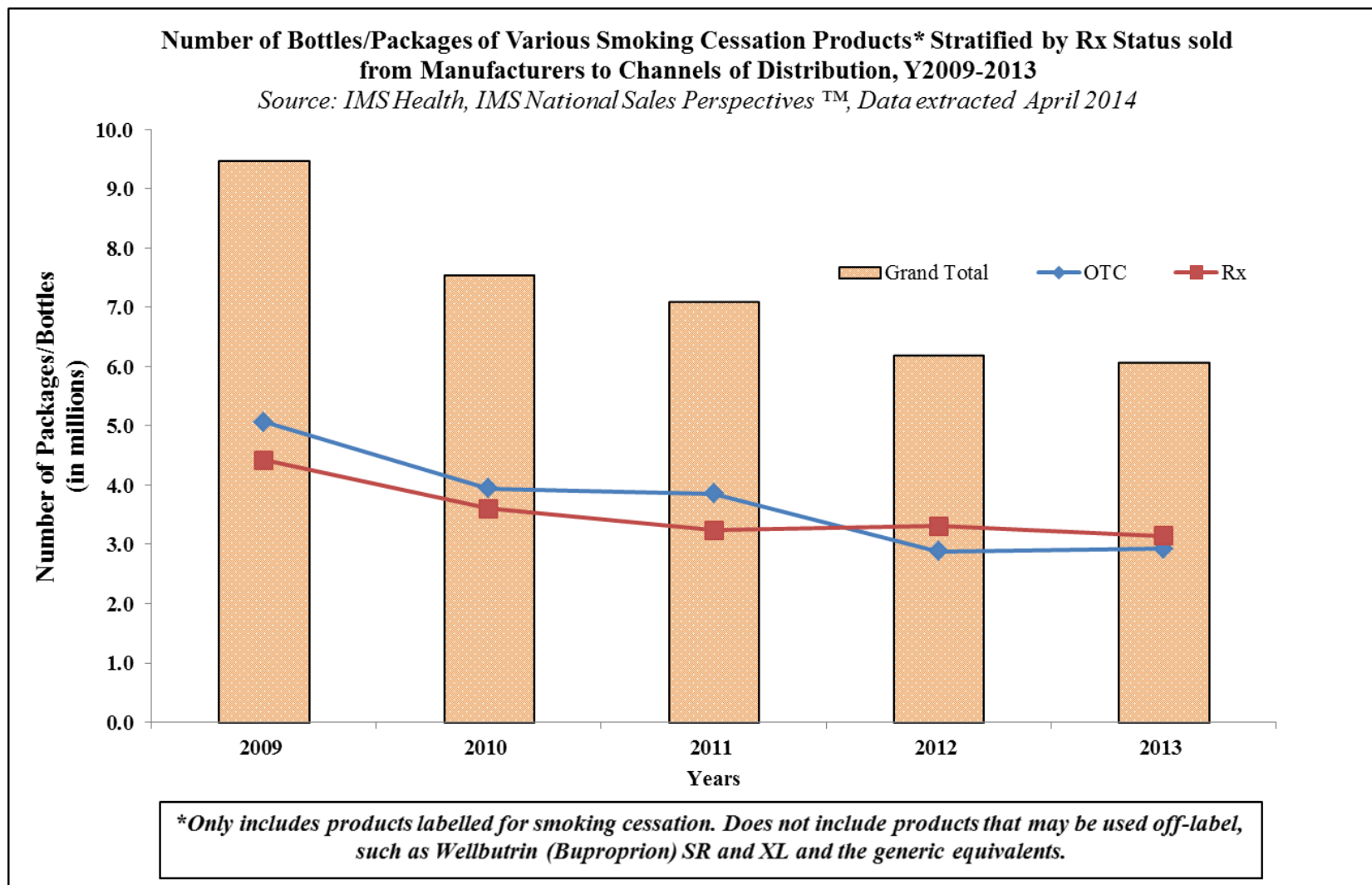


FIGURE 2.

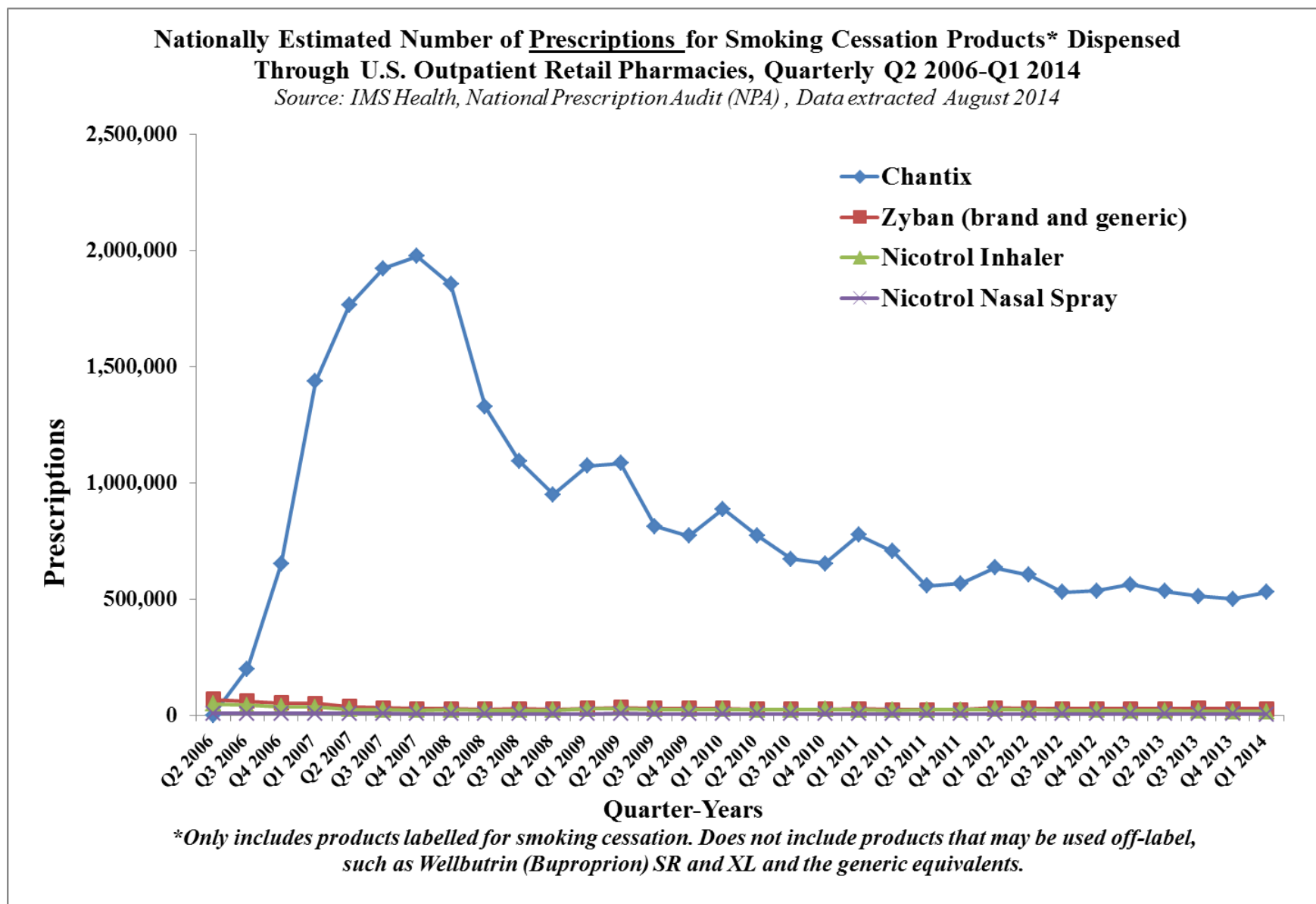


FIGURE 3.

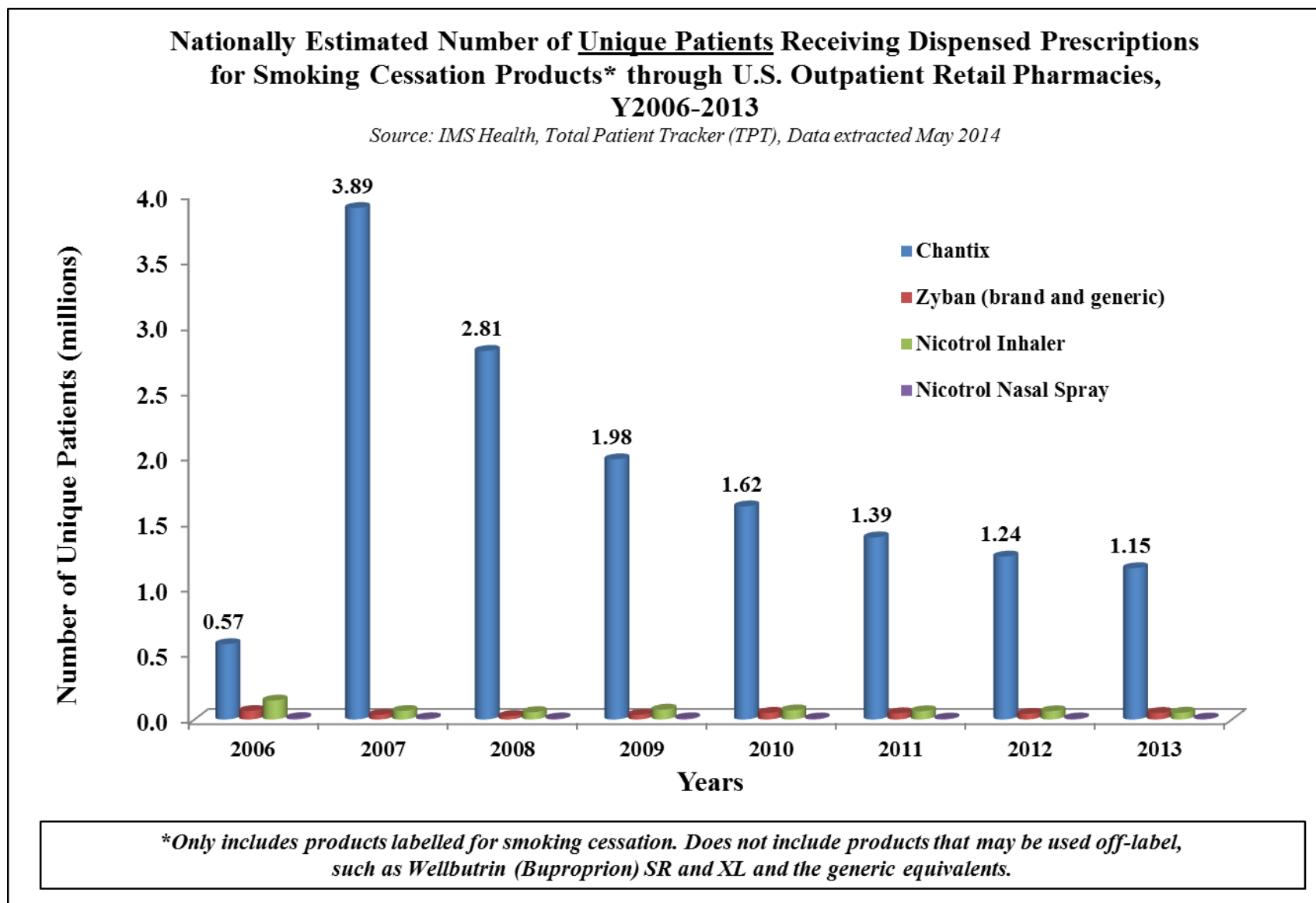
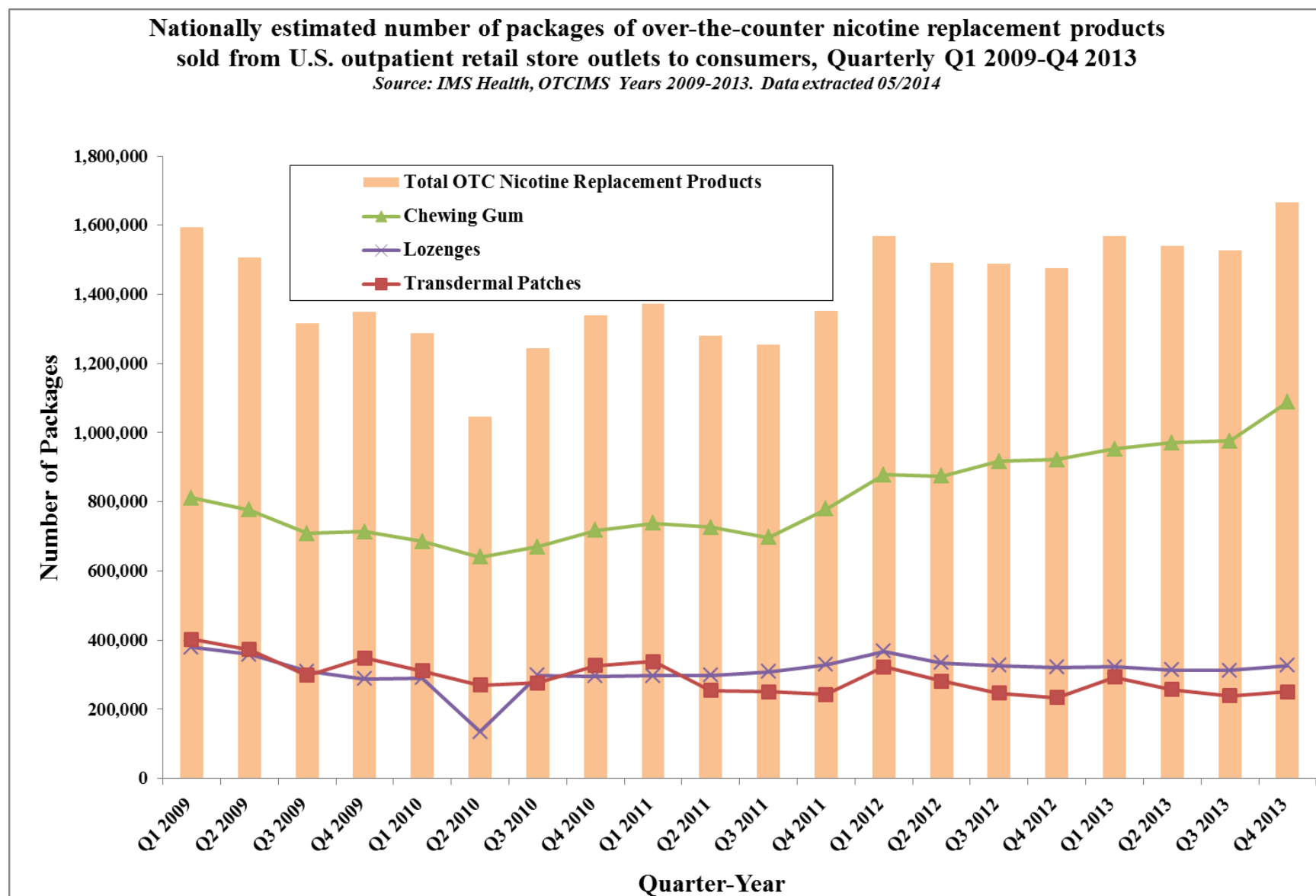


Table 1.

Nationally Estimated Number of Unique Patients Receiving Dispensed Prescriptions for Chantix (stratified by patient age and sex) through U.S. Outpatient Retail Pharmacies, Year 2006-2013																
	2006		2007		2008		2009		2010		2011		2012		2013	
	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<b>Grand Total</b>	<b>573,213</b>	<b>100.0%</b>	<b>3,894,979</b>	<b>100.0%</b>	<b>2,806,737</b>	<b>100.0%</b>	<b>1,980,783</b>	<b>100.0%</b>	<b>1,622,684</b>	<b>100.0%</b>	<b>1,385,902</b>	<b>100.0%</b>	<b>1,240,260</b>	<b>100.0%</b>	<b>1,151,841</b>	<b>100.0%</b>
0 - 17 years	983	0.2%	8,645	0.2%	6,774	0.2%	3,474	0.2%	2,028	0.1%	1,519	0.1%	1,129	0.1%	786	0.1%
18 - 24 years	9,942	1.7%	107,057	2.7%	95,915	3.4%	66,359	3.4%	54,828	3.4%	48,133	3.5%	41,735	3.4%	35,074	3.0%
25 - 44 years	161,636	28.2%	1,289,304	33.1%	1,005,722	35.8%	716,400	36.2%	634,499	39.1%	543,520	39.2%	492,616	39.7%	446,319	38.7%
45 - 64 years	334,684	58.4%	2,112,129	54.2%	1,450,289	51.7%	1,016,473	51.3%	805,569	49.6%	682,085	49.2%	605,214	48.8%	568,710	49.4%
65 years and above	66,664	11.6%	395,428	10.2%	261,516	9.3%	185,763	9.4%	132,089	8.1%	115,920	8.4%	104,866	8.5%	105,897	9.2%
Unknown age	3	0.0%	51	0.0%	31	0.0%	14	0.0%	383	0.0%	129	0.0%	5	0.0%	109	0.0%
<b>Females</b>	<b>319,750</b>	<b>55.8%</b>	<b>2,179,139</b>	<b>55.9%</b>	<b>1,523,097</b>	<b>54.3%</b>	<b>1,071,745</b>	<b>54.1%</b>	<b>867,384</b>	<b>53.5%</b>	<b>736,858</b>	<b>53.2%</b>	<b>661,645</b>	<b>53.3%</b>	<b>617,920</b>	<b>53.6%</b>
0 - 17 years	463	0.1%	3,979	0.2%	3,015	0.2%	1,419	0.1%	910	0.1%	682	0.1%	479	0.1%	289	0.0%
18 - 24 years	5,644	1.8%	59,682	2.7%	52,163	3.4%	36,195	3.4%	29,738	3.4%	25,220	3.4%	21,639	3.3%	18,050	2.9%
25 - 44 years	93,506	29.2%	731,479	33.6%	545,704	35.8%	386,064	36.0%	332,821	38.4%	281,976	38.3%	256,790	38.8%	233,557	37.8%
45 - 64 years	183,845	57.5%	1,170,568	53.7%	785,456	51.6%	550,416	51.4%	435,307	50.2%	368,391	50.0%	327,889	49.6%	309,953	50.2%
65 years and above	36,646	11.5%	223,543	10.3%	144,431	9.5%	101,537	9.5%	71,909	8.3%	63,054	8.6%	57,431	8.7%	58,477	9.5%
Unknown age		0.0%	35	0.0%	10	0.0%	9	0.0%	262	0.0%	96	0.0%		0.0%	69	0.0%
<b>Males</b>	<b>253,268</b>	<b>44.2%</b>	<b>1,713,334</b>	<b>44.0%</b>	<b>1,281,279</b>	<b>45.7%</b>	<b>907,461</b>	<b>45.8%</b>	<b>753,602</b>	<b>46.4%</b>	<b>647,519</b>	<b>46.7%</b>	<b>577,087</b>	<b>46.5%</b>	<b>532,463</b>	<b>46.2%</b>
0 - 17 years	516	0.2%	4,639	0.3%	3,730	0.3%	2,047	0.2%	1,110	0.1%	825	0.1%	629	0.1%	478	0.1%
18 - 24 years	4,283	1.7%	47,232	2.8%	43,618	3.4%	30,072	3.3%	25,018	3.3%	22,859	3.5%	20,053	3.5%	16,973	3.2%
25 - 44 years	68,050	26.9%	556,816	32.5%	459,001	35.8%	329,598	36.3%	300,975	39.9%	260,861	40.3%	235,209	40.8%	212,223	39.9%
45 - 64 years	150,770	59.5%	940,377	54.9%	663,760	51.8%	465,377	51.3%	369,410	49.0%	312,928	48.3%	276,515	47.9%	257,971	48.4%
65 years and above	29,987	11.8%	171,691	10.0%	116,972	9.1%	84,130	9.3%	60,068	8.0%	52,771	8.1%	47,315	8.2%	47,299	8.9%
Unknown age	3	0.0%	15	0.0%	14	0.0%	5	0.0%	121	0.0%	33	0.0%	5	0.0%	41	0.0%
<b>Unspecified Gender</b>	<b>181</b>	<b>100.0%</b>	<b>2,567</b>	<b>100.0%</b>	<b>2,367</b>	<b>100.0%</b>	<b>1,568</b>	<b>100.0%</b>	<b>1,630</b>	<b>100.0%</b>	<b>1,500</b>	<b>100.0%</b>	<b>1,496</b>	<b>100.0%</b>	<b>1,480</b>	<b>100.0%</b>
Source: IMS Health, Total Patient Tracker (TPT), Years 2006-2013. Data extracted August 2014. Source File: TPT 2014-749 chantix age and gender 08-13-14																
*Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study.																
** Patient age subtotals may not sum exactly due to patients aging during the study ("the cohort effect"), and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.																

Figure 4.



## **APPENDIX 2: Drug Use Database Descriptions.**

### **IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### **IMS Health, National Prescription Audit**

The National Prescription Audit (NPA™) has been the industry standard source of national prescription activity since 1952. NPA measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

### **IMS, Vector One®: Total Patient Tracker (TPT)**

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

### **OTC International Market Tracking (OTCIMS)**

The OTC International Market Tracking (OTCIMS) platform can provide the FDA with highly accurate retail sales data for all OTC drugs. OTCIMS tracks key molecular data characteristics, strength of active ingredients; dosage form; and size of drug products by mL, number of tablets/capsules, and/or total doses available. OTCIMS data is delivered quarterly in CD format and accessible through a secure, stand-alone desktop application called Dataview™.



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Pharmacovigilance and Epidemiology**

**Pharmacovigilance Review**

**Date:** 9/4/2014

**Reviewer:** Martin Pollock, PharmD, Safety Evaluator  
Division of Pharmacovigilance II

**Team Leader:** Sara Camilli, PharmD, Safety Evaluator Team Leader  
Division of Pharmacovigilance II

**Division Director:** Scott Proestel, MD, Director  
Division of Pharmacovigilance II

**Product Name:** Chantix (varenicline tartrate)

**Subject:** Neuropsychiatric events

**Application Type/Number:** NDA 21928

**Applicant/Sponsor:** Pfizer

**OSE RCM #:** 2014-1620

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## EXECUTIVE SUMMARY

This document provides recent (2013-2014) case-level data for varenicline and serious neuropsychiatric adverse events, as requested by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) in support of an upcoming Advisory Committee. This is an update from our two prior reviews completed in 2008.<sup>1,2</sup>

In April 2014, Pfizer submitted a varenicline supplement that included a proposed labeling change for the addition of information from observational studies and clinical trial meta-analyses. Pfizer's supplement concludes that from this new data, there is not a significant neuropsychiatric event risk with varenicline and that therefore the Boxed Warning is no longer justified. An FDA Advisory Committee will convene on 10/16/14 to discuss this new data and potential removal of the Boxed Warning.<sup>3</sup>

We found 105 FAERS cases of varenicline and serious psychiatric events from the time period of 1/1/13 to 6/30/14 where a significant behavior change in association with varenicline was stated or implied. These cases consisted of suicidality, psychosis/mania, aggression or other neuropsychiatric events, and were consistent with the findings of our 2008 reviews that led to the current Boxed Warning. Characteristics of the events in this review as well as the prior reviews<sup>1,2</sup> include:

- Neuropsychiatric events occurred in patients with and without a history of psychiatric disorders.
- Events occurred while patients were on varenicline and following varenicline use.
- In addition to consumer reporters, there were also healthcare care professional reporters.
- Positive dechallenges, a relatively short time to event onset (median 10 days), and positive rechallenges.

Based upon this updated review, no changes in the varenicline label for serious neuropsychiatric events in the post marketing setting are recommended.

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<sup>1</sup>Pollock M, Mosholder A, Lee J, Governale L. Suicidality associated with varenicline, bupropion, and nicotine transdermal patch. 7/16/08; OSE RCM #2007-2425.

<sup>2</sup>Pollock M, Mosholder A, Ju J. Psychiatric events (including suicides) associated with varenicline and bupropion. 12/8/08; OSE RCM# 2008-1291.

<sup>3</sup>Notice of Meeting: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee; *Federal Register* 4/25/14; Vol 79, No 80; page 22995-6. 4/25/14.

# 1 INTRODUCTION

## 1.1 BACKGROUND

This document provides recent case-level data for varenicline and neuropsychiatric adverse events, as requested by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) in support of the October 16, 2014 Advisory Committee. This is an update to our two prior reviews completed in 2008<sup>4,5</sup> and is restricted to serious reports of select neuropsychiatric adverse events with an event date from January 2013 through June 2014.

Neuropsychiatric events associated with varenicline have been of interest for the past seven years. In 2008, the Division of Pharmacovigilance's reviews found a signal for psychiatric events in FDA's Adverse Event Reporting System (FAERS). These reviews described cases of suicidality,<sup>4</sup> psychosis/mania,<sup>5</sup> aggression<sup>5</sup> and other neuropsychiatric events<sup>5</sup> (e.g., depression and personality change) with varenicline. Regulatory actions taken after the FAERS reviews included an FDA Early Safety Communication (2007)<sup>6</sup> and augmentation of the varenicline label for such events, culminating in a Boxed Warning in 2009.<sup>7</sup>

In April 2014, Pfizer submitted a varenicline supplement that included a proposed labeling change for the addition of information from observational studies and clinical trial meta-analyses. Pfizer's supplement concludes that from this new data, there is not a significant neuropsychiatric event risk with varenicline and that therefore the Boxed Warning is no longer justified. An FDA Advisory Committee will convene on 10/16/14 to discuss this new data and potential removal of the Boxed Warning.<sup>8</sup>

In May 2014, in support of a Center Director briefing, DPV II provided FAERS high level data for domestic reports of neuropsychiatric adverse events associated with varenicline.<sup>9</sup> This data showed that FDA continues to receive serious neuropsychiatric adverse events reports in association with varenicline use.

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<sup>4</sup>Pollock M, Mosholder A, Lee J, Governale L. Suicidality associated with varenicline, bupropion, and nicotine transdermal patch. 7/16/08; OSE RCM #2007-2425.

<sup>5</sup>Pollock M, Mosholder A, Ju J. Psychiatric events (including suicides) associated with varenicline and bupropion. 12/8/08; OSERCM# 2008-1291.

<sup>6</sup>Early Communication about an Ongoing Safety Review of Varenicline (marketed as Chantix); 11/20/07<http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/drugsafetyinformationforhealthcareprofessionals/ucm070765.htm>.

<sup>7</sup>Public Health Advisory: FDA Requires New Boxed Warnings for the Smoking Cessation Drugs Chantix and Zyban; 7/1/09' <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/drugsafetyinformationforhealthcareprofessionals/publichealthadvisories/ucm169988.htm>

<sup>8</sup>Notice of Meeting: Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee; *Federal Register* 4/25/14; Vol 79, No 80; page 22995-6. 4/25/14.

<sup>9</sup>Camilli S. Varenicline: Neuropsychiatric Events Crude Counts 2008-2013; 5/16/14; OSE RCM 2014-749.

## 1.2 REGULATORY HISTORY

Varenicline (Chantix) is a partial neuronal nicotinic acetylcholine receptor agonist indicated for use as an aid to smoking cessation treatment. Varenicline (0.5 mg and 1 mg tablets) was approved May 10, 2006.

## 1.3 PRODUCT LABELING

Psychiatric events are mentioned in the varenicline labeling in the following sections: Boxed Warning, Warnings and Precautions (5.1), Adverse Reactions (6.1, 6.2), Patient counseling information (17.7), and the Medication Guide. See Appendix 7.1 for the labeling text.

## 2 METHODS AND MATERIALS

### 2.1 CASE DEFINITION

Include reports:

- New onset behavior change (patient had no prior psychiatric history) OR
- Worsening of a pre-existing psychiatric condition that appeared stable prior to varenicline administration

Exclude reports:

- No mention or implication of an adverse event in association with varenicline use
- Confounded by concomitant medical conditions or potential drug interactions
- Event confined to sleep disturbances (including abnormal dreams)
- Confounded by concomitant use of alcohol

### 2.2 FAERS SEARCH STRATEGY

The FAERS database was searched with the strategy described in Table 1.

<b>Table 1. FAERS Search Strategy*</b>	
Date of search	7/31/14
Time period of search for <i>event date</i>	1/1/13-6/30/14
Product Terms (as active ingredient)	Varenicline; Varenicline HCl
MedDRA Search Terms	Psychiatric events, <sup>†</sup> grouped for: Suicidality Psychosis/mania Aggression Miscellaneous See Appendix 7.2 for listing of all terms.
Outcome	Serious

\*See 7.3 for description of the FAERS database.

<sup>†</sup>As per DPV original 2008 reviews of varenicline and psychiatric events (Footnotes 1 and 2). A search was also done for all varenicline reports in the database (i.e., any event).

### 3 RESULTS

#### 3.1 FAERS CASE SELECTION

FAERS contained 840 serious varenicline reports (for any event) with an event date between 1/1/13 and 6/30/14. Almost half (n=345; 41%) of these reports were neuropsychiatric events. The trend for month and year of the reports is shown in Appendix 7.4. We searched the narratives of the 345 neuropsychiatric reports for words/phrases that implied a behavioral change following varenicline administration (Appendix 7.5).

The narrative search yielded 259 reports. After examining these reports and applying the case definition in Section 2 and accounting for duplicate reports, 105 cases were included in the case series of neuropsychiatric events with varenicline use (see Figure 1).

**Figure 1. FAERS Case Selection**

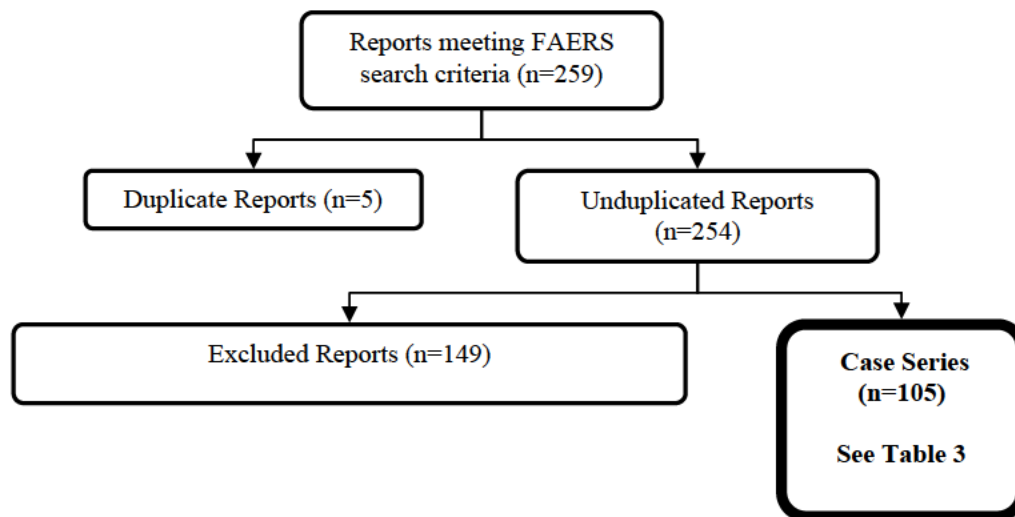


Table 2 summarizes the 105 FAERS cases of neuropsychiatric events reported with varenicline for this case series. Appendix 7.6 lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 105 cases in this case series.

<b>Table 2. Descriptive characteristics of psychiatric events reported with varenicline use, event date from 1/1/13 to 6/30/14 (N=105)</b>		
Characteristic	New onset (n=71)	Worsening of pre-existing condition (n=34)
Sex		
Male (n=50)	36	14
Female (n=53)	34	19
Unknown (n=2)	1	1
Age <sup>†</sup> (years)		
Mean (40.5)	39.8	41.9
Median (39)	37	40.5
Range (18 to 73)	18 to 73	21 to 62
Event type <sup>†</sup>		
Suicidality (n=47)	25	22
Psychosis/mania (n=25)	18	7
Aggression (n=31)	26	5
Other (n=94)	64	30
See Appendix 7.7 for PT listings		
Event Onset <sup>‡</sup>		
While on varenicline (n=99)	n=67	n=32
Known (n=72)	n=48	n=24
Mean (days) (15.4)	16.1	14.0
Median (days) (9.75)	10	9
Range (days) (1-90)	1-90	1-45
After varenicline discontinuation (n=6)	n=4	n=2
One day (1)	1	0
Two days (1)	0	1
Three days (3)	2	1
Seven days (1)	1	0
Country		
USA (n=56)	37	19
Foreign (n=49)	34	15
Report type		
Direct (n=19)	15	4
Expedited (15-Day) (n=63)	40	23
Periodic (n=23)	16	7
Reporter		
Consumer (n=63)	46	17
Healthcare professional (n=42)	25	17
Outcome (regulatory) <sup>+</sup>		
Death (n=6)	4	2
Hospitalization (n=11)	6	5
Life-threatening (n=10)	6	4
Disability (n=13)	11	2
Other (n=86)	57	29

<b>Table 2. Descriptive characteristics of psychiatric events reported with varenicline use, event date from 1/1/13 to 6/30/14 (N=105)</b>		
Characteristic	New onset (n=71)	Worsening of pre-existing condition (n=34)
Outcomes, non-regulatory; for non-fatal (n=99)		
Varenicline discontinued		
No (n=6)	3	3
Unknown (n=12)	7	5
Yes (n=81)	57	24
Positive dechallenge		
Yes (n=30)	20	10
No (n=22)	17	5
Not applicable <sup>†</sup> (n=6)	4	2
Unknown (n=21)	15	6
Positive rechallenge <sup>‡</sup>	1	1
Recovery		
Yes (n=38)	25	13
No (n=20)	16	4
Unknown (41)	26	15
Time of event	See Appendix 7.8 for graph of cases by event year and quarter	
Dose (mg/day)		
0.5 (n=1)	1	0
1 (n=8)	6	2
2 (n=42)	31	11
Unknown (n=54)	33	21
Smoking status at time of event		
Smoking (n=9)	9	0
Not smoking (n=8)	7	1
Unknown (n=88)	55	33

<sup>†</sup>Age known for 97 cases (new onset, n=66; worsening, n=31).

<sup>‡</sup>Event onset known for 72 cases (new onset, n=48; worsening, n=24).

<sup>†</sup>Not mutually exclusive.

<sup>‡</sup>Event occurred after varenicline was discontinued.

<sup>‡</sup>Mentioned in Appendix 7.8 case index # 15 and 20.

## REPRESENTATIVE CASES

We have selected 20 cases as representative across the 4 event categories (suicidality, psychosis/mania, aggression and other neuropsychiatric adverse events). These cases are presented in Appendix 7.8.

## 4 DISCUSSION

An Advisory Committee will convene on October 16, 2014, to discuss the existing neuropsychiatric Boxed Warning for varenicline. The Boxed Warning was added following varenicline approval because of postmarketing FAERS reports. <sup>Error! Bookmark not defined.,Error!</sup>

<sup>Bookmark not defined.</sup> This update supports that we continue to receive reports of serious



neuropsychiatric events in association with varenicline use. One compelling characteristic of the reports we found in 2008 was the significant behavior changes that the patients experienced in association with varenicline. In our case series for this review (n=105) we captured only events reporting significant behavior change (e.g., reports<sup>10</sup> that stated “nothing like this has ever happened before” or “pre-existing depression and chronic paranoid schizophrenia were noted to be stable 6 months prior to starting varenicline”). Many of the excluded cases for this case series would have been included based upon our 2008 review criteria. Therefore, although this update assessed a short period of time, it also provides a more selective case series.

We note other characteristics in our case series that are similar to the 2008 review and consistent with the varenicline labeling, including:

- Neuropsychiatric events occurred in patients with and without a history of psychiatric disorders.
- Events occurred while patients were on varenicline as well as shortly following varenicline use.
- In addition to consumer reporters, there were also healthcare care professional reporters.
- Positive dechallenges, a relatively short time to event onset (median 10 days), and positive rechallenges.

Although we grouped the neuropsychiatric events into 4 categories (Appendix 7.2), Table 2 shows the distribution of these categories to be non-mutually exclusive. In fact, the majority (75/105, 71%) of our case series had events from two or more of the categories. The top 2 events (Appendix 7.7) were depression and suicidal ideation, which may be closely associated. Consistent with the 2008 review, in addition to suicidal ideation, this case series identified patients with more severe consequences (e.g., completed suicide and suicide attempt).

## **5 CONCLUSION**

In a recent 18 month period (January 2014 through June 2014) we found 105 FAERS cases of serious neuropsychiatric events in association with varenicline use. These cases included suicidality, psychosis/mania, aggression, or other neuropsychiatric events, and were consistent with what was observed in our initial 2008 reviews of this safety issue.

## **6 RECOMMENDATIONS**

Based upon this updated review, no changes in the varenicline labeling for serious neuropsychiatric events are recommended.

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<sup>10</sup>Examples for two different patients from Appendix 7.9

## 7 APPENDICES

### 7.1 VARENICLINE LABELING (AS OF 2/19/13) FOR PSYCHIATRIC EVENTS<sup>11</sup>

#### **WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS**

Serious neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. *[see Warnings and Precautions (5.1) and Adverse Reactions 6.2)]*

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Neuropsychiatric Symptoms and Suicidality

Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX [see Boxed Warning and Adverse Reactions (6.2)].

<sup>11</sup>Labeling from Patient counseling information (17.7) and the (patient) Medication guide is not presented.

These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients has not been established. Limited data are available from a single smoking cessation study in patients with stable schizophrenia or schizoaffective disorder [see Adverse Reactions (6.1)].

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, depressed mood, changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve. The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

## 5.5 Accidental Injury

There have been postmarketing reports of traffic accidents, near-miss incidents in traffic, or other accidental injuries in patients taking CHANTIX. In some cases, the patients reported somnolence, dizziness, loss of consciousness or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. Advise patients to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (HLGTs  $\geq$  5% of patients in the 1 mg BID CHANTIX Group and more commonly than placebo and PT  $\geq$  1% in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	CHANTIX 0.5 mg BID N=129	CHANTIX 1 mg BID N=821	Placebo N=805
<b>PSYCHIATRIC DISORDERS</b>			
Sleep Disorder/Disturbances			
Insomnia **	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
<b>NERVOUS SYSTEM</b>			
Headaches			
Headache	19	15	13
Neurological Disorders			

NEC			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
GENERAL DISORDERS			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6

\*\*Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

In the trial of patients with stable schizophrenia or schizoaffective disorder, 128 smokers on antipsychotic medication were randomized 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up. The most common adverse events in patients taking varenicline were nausea (24% vs. 14.0% on placebo), headache (11% vs. 19% on placebo) and vomiting (11% vs. 9% on placebo). Among reported neuropsychiatric adverse events, insomnia was the only event that occurred in either treatment group in  $\geq 5\%$  of subjects at a rate higher in the varenicline group than in placebo (10% vs. 5%). These common and neuropsychiatric adverse events occurred on treatment or within 30 days after the last dose of study drug. There was no consistent worsening of schizophrenia in either treatment group as measured by the Positive and Negative Syndrome Scale. There were no overall changes in extra-pyramidal signs, as measured by the Simpson-Angus Rating Scale. The Columbia-Suicide Severity Rating Scale was administered at baseline and at clinic visits during the treatment and non-treatment follow-up phases. Over half of the patients had a lifetime history of suicidal behavior and/or ideation (62% on varenicline vs. 51% on placebo), but at baseline, no patients in the varenicline group reported suicidal behavior and/or ideation vs. one patient in the placebo group (2%). Suicidal behavior and/or ideation were reported in 11% of the varenicline-treated and 9% of the placebo-treated patients during the treatment phase. During the post-treatment phase, suicidal behavior and/or ideation were reported in 11% of patients in the varenicline group and 5% of patients in the placebo group. Many of the patients reporting suicidal behavior and ideation in the follow-up phase had not reported such experiences in the treatment phase. However, no new suicidal ideation or behavior emerged in either treatment group shortly (within one week) after treatment discontinuation (a phenomenon noted in post-marketing reporting). There were no completed suicides. There was one suicide attempt in a varenicline-treated patient. The limited data available from this single smoking cessation study are not sufficient to allow conclusions to be drawn.

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

**Nervous System Disorders.**<sup>12</sup> *Frequent:* disturbance in attention, *Infrequent:* amnesia, psychomotor hyperactivity, *Rare:* mental impairment, psychomotor skills impaired

**Psychiatric Disorders.** *Infrequent:* disorientation, dissociation, libido decreased, mood swings, thinking abnormal. *Rare:* bradyphrenia, euphoric mood

## 6.2 Postmarketing Experience

The following adverse events have been reported during post-approval use of CHANTIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide in patients attempting to quit smoking while taking CHANTIX [see Boxed Warning, Warnings and Precautions (5.1)]. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking.

<sup>12</sup>This is not the complete list. Events that are not psychiatric-related (e.g. migraine, restless leg syndrome) are not listed.

## 7.2 MEDDRA SEARCH TERMS FOR PSYCHIATRIC EVENTS\*

<b>Suicidality</b>	<b>Psychosis Mania</b>	<b>Aggression/Violent Behavior</b>	<b>Miscellaneous</b>
Suicidal and self-injurious behavior NEC (HLGT)	Mania	Aggression	Abnormal behavior
Depression suicidal	Paranoia	Belligerence	Amnestic symptoms (HLT)
Gun shot wound	Catatonia	Anger	Confusional state
Intentional drug misuse	Hypomania	Hostility	Mood alterations with depressive symptoms (HLT)
Overdose	Schizotypal personality disorder	Physical assault	Depression
	Schizophrenia and other psychotic disorders (HLGT)	Sexual abuse	Major depression
	Delusion symptoms (HLT)	Homicide	Disorientation
	Perception disturbances (HLT)	Imprisonment	Emotional disorder
	Bipolar disorders(HLT)	Homicidal ideation	Emotional distress
	Schizoid personality disorder		Feeling abnormal
	Paranoid personality disorder		Mood altered
			Mood swings
			Personality change
			Thinking abnormal
			Anxiety disorders with symptoms (HLGT)
			Trichotillomania
			Sleep disorder
			Tic disorders (HLT)

\* All events are MedDRA Preferred Terms, unless otherwise indicated.  
MedDRA = medical dictionary for regulatory activities

### **7.3 FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)**

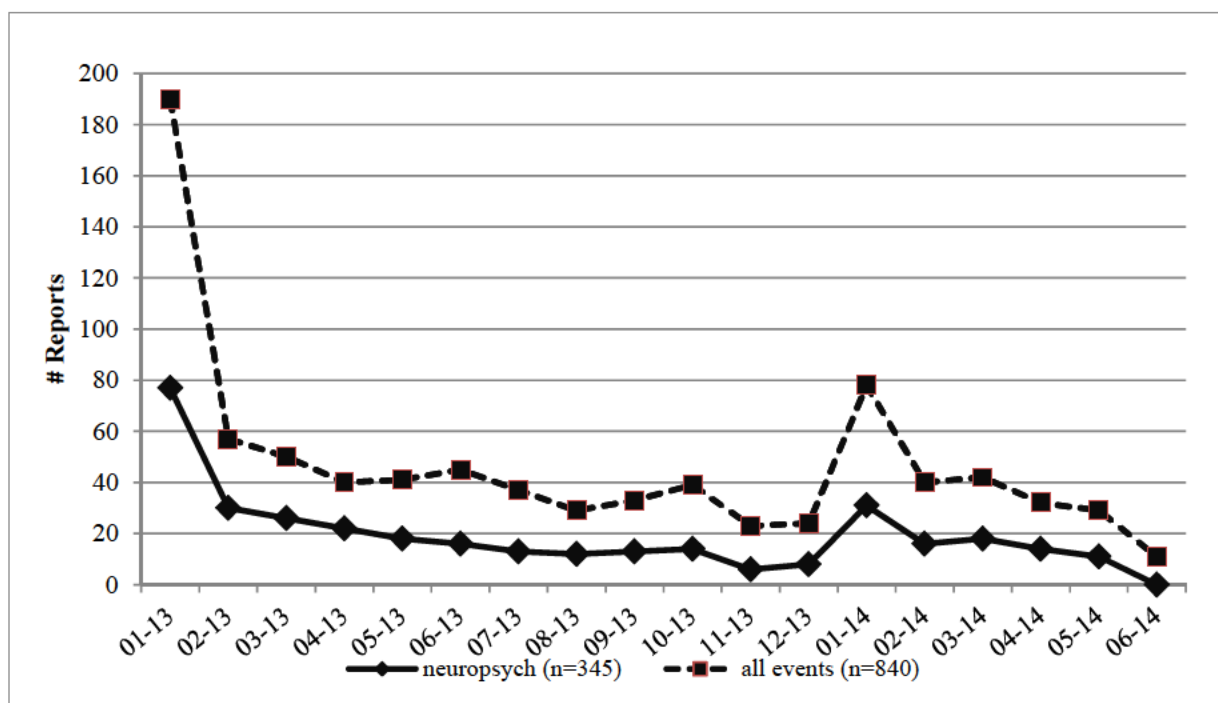
#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

#### 7.4 FAERS SERIOUS REPORTS FOR VARENICLINE (ALL (N=840) AND NEUROPSYCHIATRIC (N=345) REPORTS) BY MONTH AND YEAR, EVENT DATE JANUARY 2013 THROUGH JUNE 2014



January 2013 (n=190 and n=77 for all and neuropsychiatric reports respectively) and January 2014 (n=78 and n=31 respectively) are most likely overstated. Most (738/840 [89%] and 288/345 [83%]) of the reports are manufacturer submitted. In some, the reporter stated that the event occurred in 2013 or 2014, without specifying the month and or day. The manufacturer would then code the event date of '1/1/13' or '1/1/14' respectively. Upon individual review, when DPV encountered instances like this, if possible, the event dates were re-defined to be more specific.

There was a decrease in June 2014 (n=3 neuropsychiatric), compared to February to May (range of 11 to 18 reports/month; similar trend for all reports). However, this also may be an artifact because of the lag period (e.g., one month or more) between the occurrence of an event and report submission to FAERS.

## 7.5 NARRATIVE SEARCH TERMS THAT MAY IMPLY A DRAMATIC BEHAVIORAL CHANGE POST VARENICLINE ADMINISTRATION

Index	Key term	Related terms also captured	Index	Key term	Related terms also captured
1	never		11	like	not like
2	change		12	past	
3	different		13	control	
4	worse	worsen	14	person	personality
5	unusual		15	self	himself, herself
6	unable		16	character	
7	wrong		17	strange	
8	right	not right	18	beh	behavior, behaviour
9	feel	feeling	19	normal	abnormal
10	felt				



## 7.6 FAERS CASE NUMBERS, VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS FOR VARENICLINE AND NEUROPSYCHIATRIC EVENT CASE SERIES (N=105)

Case Id	Version	Mfr control #
9027283	1	ZA-PFIZER INC-2013024032
9052438	2	ZA-PFIZER INC-2013043961
9053352	1	CA-PFIZER INC-2013047040
9081249	1	US-PFIZER INC-2013060874
9089169	2	ZA-PFIZER INC-2013041621
9097892	3	US-PFIZER INC-2013056914
9112792	1	US-PFIZER INC-2013054929
9117904	1	GB-PFIZER INC-2013048191
9118004	1	US-PFIZER INC-2013049185
9121298	1	ZA-PFIZER INC-2013065985
9154559	1	Direct report
9200357	1	GB-PFIZER INC-2013100348
9200507	1	US-PFIZER INC-2013102347
9201423	1	GB-PFIZER INC-2013101451
9210428	1	GB-PFIZER INC-2013106846
9222372	1	GB-PFIZER INC-2013112590
9247980	1	Direct report
9248035	3	US-PFIZER INC-2013125393
9257448	1	GB-PFIZER INC-2013130874
9257503	2	US-PFIZER INC-2013131196
9258586	1	Direct report
9286403	1	GB-PFIZER INC-2013144785
9288573	1	GB-PFIZER INC-2013148672
9297781	1	US-PFIZER INC-2013153569
9297846	1	US-PFIZER INC-2013153414
9312024	1	GB-PFIZER INC-2013159428
9315299	2	GB-TEVA-407965ISR
9322113	1	GB-PFIZER INC-2013165592
9322131	1	US-PFIZER INC-2013164918
9324928	1	GB-PFIZER INC-2013097294
9344144	1	GB-PFIZER INC-2013175123
9349103	1	GB-PFIZER INC-2013177725
9371705	2	US-PFIZER INC-2013191599
9377042	1	GB-PFIZER INC-2013190931
9378888	1	US-PFIZER INC-2013194474
9379438	1	AU-PFIZER INC-2013191765
9386854	1	US-PFIZER INC-2013200279
9401976	1	US-PFIZER INC-2013204732
9415503	1	GB-PFIZER INC-2013212812
9416696	2	GB-PFIZER INC-2013213999
9419518	1	GB-PFIZER INC-2013214035
9434498	1	Direct report
9437068	1	AU-PFIZER INC-2013221542
9444047	1	Direct report
9450022	2	CA-PFIZER INC-2013229008
9450409	1	US-PFIZER INC-2013230210
9464636	2	GB-PFIZER INC-2013237517

Case Id	Version	Mfr control #
9465821	1	US-PFIZER INC-2013240331
9475780	1	US-PFIZER INC-2013244820
9475974	1	GB-PFIZER INC-2013243636
9507819	4	PA-PFIZER INC-2013258240
9515455	1	US-PFIZER INC-2013261176
9526570	1	US-PFIZER INC-2013264958
9556834	1	US-PFIZER INC-2013276635
9559809	3	AU-PFIZER INC-2013278483
9608286	1	US-PFIZER INC-2013285799
9612612	1	GB-PFIZER INC-2013286113
9617236	3	US-ABBVIE-13P-163-1154501-00
9637835	1	US-PFIZER INC-2013301973
9644927	1	US-PFIZER INC-2013304715
9647953	1	Direct report
9657214	1	US-PFIZER INC-2013303865
9667718	3	US-PFIZER INC-2013311053
9667868	1	NO-PFIZER INC-2013312265
9674228	1	GB-PFIZER INC-2013314753
9691013	1	CA-PFIZER INC-2013322211
9711960	1	Direct report
9731985	4	JP-PFIZER INC-2013334587
9740982	1	GB-PFIZER INC-2013350343
9771125	1	GB-PFIZER INC-2013362023
9783562	1	US-PFIZER INC-2013368152
9793207	1	Direct report
9816142	2	US-PFIZER INC-2014010297
9894869	2	GB-PFIZER INC-2014023972
9915951	1	Direct report
9918856	2	AU-PFIZER INC-2014027229
9970724	1	Direct report
9991587	1	US-PFIZER INC-2014068571
9992420	1	US-PFIZER INC-2014068519
9998990	1	Direct report
10011828	1	GB-PFIZER INC-2014067811
10015356	1	US-PFIZER INC-2014076583
10031913	2	HU-PFIZER INC-2014080047
10037625	1	Direct report
10039587	2	CA-PFIZER INC-2014052540
10050322	1	Direct report
10051396	2	US-PFIZER INC-2014091450
10066963	1	GB-PFIZER INC-2014096452
10068819	2	US-PFIZER INC-2014095874
10076592	1	US-PFIZER INC-2014103116
10078998	1	Direct report
10082133	1	Direct report
10089754	2	US-PFIZER INC-2014110427
10102898	1	GB-PFIZER INC-2014110001
10132026	1	NO-PFIZER INC-2014115935
10154561	1	US-PFIZER INC-2014120529
10156764	1	Direct report
10182580	1	Direct report

Case Id	Version	Mfr control #
10185115	1	Direct report
10188248	1	Direct report
10202760	1	GB-PFIZER INC-2014143504
10217162	1	GB-PFIZER INC-2014150096
10219909	1	GB-PFIZER INC-2014151277
10243650	1	US-PFIZER INC-2014167266
10262011	2	CA-PFIZER INC-2014069840

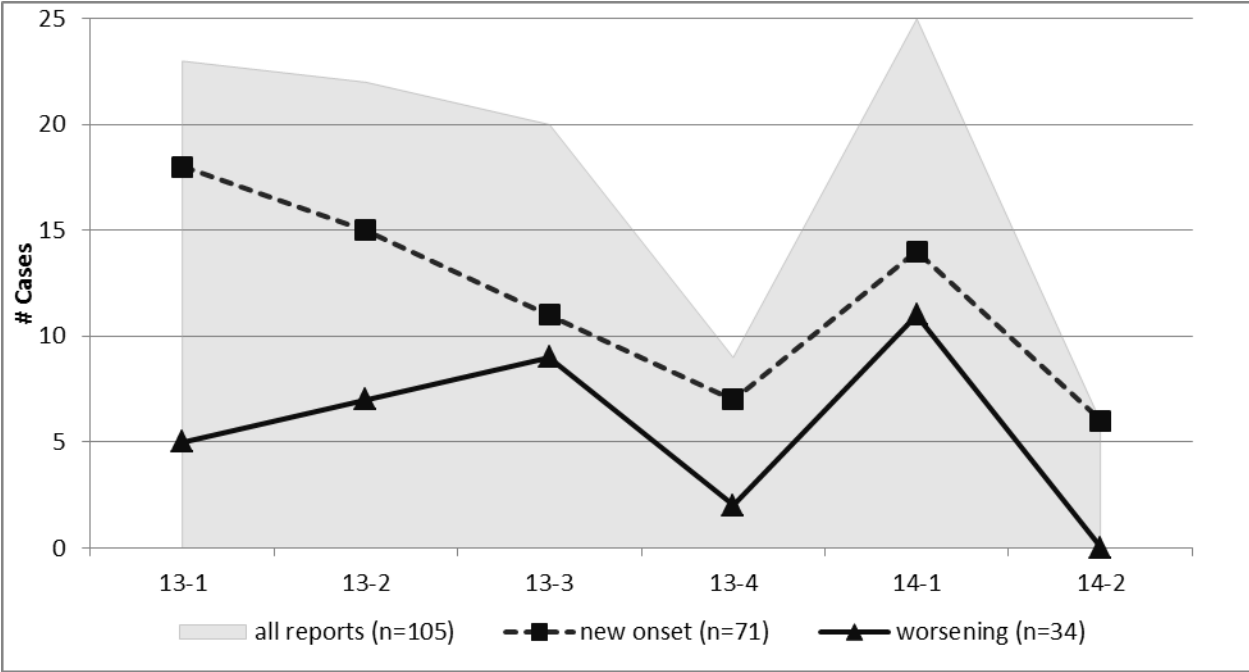
## 7.7 MEDDRA PREFERRED TERMS FOR VARENICLINE AND NEUROPSYCHIATRIC EVENT CASE SERIES (N=105)\*

Rank (for top 10)	Preferred term	Event category	N
2	Suicidal ideation	suicidality	33
	Completed suicide	suicidality	5
	Intentional self-injury	suicidality	4
	Suicide attempt	suicidality	4
	Suicidal behaviour	suicidality	3
	Self-injurious ideation	suicidality	2
	Overdose	suicidality	1
	Self injurious behaviour	suicidality	1
	Paranoia	psychosis/mania	11
	Hallucination	psychosis/mania	7
	Psychotic disorder	psychosis/mania	3
	Hallucination, auditory	psychosis/mania	2
	Hallucination, visual	psychosis/mania	2
	Mania	psychosis/mania	2
	Bipolar disorder	psychosis/mania	1
	Delusion	psychosis/mania	1
	Delusion of grandeur	psychosis/mania	1
	Delusional perception	psychosis/mania	1
	Derealisation	psychosis/mania	1
	Hallucinations, mixed	psychosis/mania	1
	Illusion	psychosis/mania	1
	Psychotic behaviour	psychosis/mania	1
	Schizophreniform disorder	psychosis/mania	1
5	Anger	aggression	20
8	Aggression	aggression	15
	Hostility	aggression	3
	Homicidal ideation	aggression	2
	Physical assault	aggression	1
1	Depression	other	38
3	Anxiety	other	24
4	Feeling abnormal	other	22
6	Abnormal behaviour	other	18
7	Depressed mood	other	16
9	Personality change	other	14
10	Mood altered	other	12
	Agitation	other	11
	Thinking abnormal	other	8
	Emotional disorder	other	6
	Fear	other	6
	Confusional state	other	5
	Memory impairment	other	5
	Mood swings	other	5
	Tearfulness	other	5

Rank (for top 10)	Preferred term	Event category	N
	Negative thoughts	other	4
	Panic attack	other	4
	Depressive symptom	other	3
	Sleep disorder	other	3
	Amnesia	other	2
	Decreased interest	other	2
	Feeling of despair	other	2
	Nervousness	other	2
	Stress	other	2
	Emotional distress	other	1
	Feeling guilty	other	1
	Feelings of worthlessness	other	1
	Obsessive thoughts	other	1
	Panic reaction	other	1
	Tension	other	1

\* Rows in GREY are top 10 as listed in Rank

**7.8 VARENICLINE AND NEUROPSYCHIATRIC EVENTS CASE SERIES (N=105) BY EVENT YEAR AND QUARTER (2013 – 2014)**



## 7.9 REPRESENTATIVE FAERS CASES FOR VARENICLINE AND NEUROPSYCHIATRIC EVENTS (N=20)

Case Index	Event Category	Key Event	Other Events	Case ID; Age/Sex	Report Type; Country; Reporter <sup>13</sup>	Onset (days); Positive Dechallenge; Event Recovery, Daily Dose (mg)	Outcomes
1	suicidality, new onset	completed suicide	none	9444047; 23M	Direct; USA; CON	5; NA; no ;unk	DE,LT,OT
<i>Young adult using Chantix, on day 5 of use, took his own life. This was a college student within 10 weeks of graduating. Had a job lined up and just wanted to quit smoking before starting a new career. He was a focused student, well liked and not suicidal.</i>							
2	suicidality, new onset	suicidal ideation	abnormal behavior, aggression, anger, anxiety, confusional state, depressed mood, dizziness, fatigue, feeling abnormal, hallucination, insomnia, mania, paranoia	10156764; 25F	Direct; USA; CON	90; no; no ;unk	DS,HO,OT
<i>Patient was on Chantix for 3 months and "everything was okay." Suddenly she quit her job and family and friends noticed a change in behavior, described as "cutting communications with friends and coworkers." She sought medical care after experiencing suicidal thoughts, hallucinations, and insomnia. Patient was informed that she was experiencing side effects from Chantix medication. Patient subsequently presented to the ER and was hospitalized for an unknown reason and is taking "four different medications to counteract the effects that Chantix has had on my body." The side effects she experienced include "fatigue, dizziness, depressed mood, suicidal thoughts and actions toward myself and my young child, acute anxiety, vision problems (attributed to taking another medication associated still with the use of Chantix) hopelessness, hallucinations, aggression, anger, mania, abnormal sensations, hallucinations, paranoia, and severe confusion."</i>							
3	suicidality, worsening	completed suicide	abnormal behavior, insomnia	9379438; 22M	Expedited (15-Day); foreign; CON	14; NA; no ;unk	DE
<i>Patient experienced bizarre behavior soon after starting Chantix, described as "asking for tape so he could tape up his room so no one could get in," and "only slept when his brother was awake with him." The patient's mother reports her son "sitting on a cushion outside his door with a chainsaw playing in the background" and remembers him making odd comments, including alluding to his funeral. Two weeks after starting Chantix, he hung himself. Medical history included post-traumatic stress disorder and anxiety disorder, both from an unknown date. The patient was not on any concomitant medications.</i>							

<sup>13</sup>CON=consumer; HCP=Healthcare professional

Case Index	Event Category	Key Event	Other Events	Case ID; Age/Sex	Report Type; Country; Reporter <sup>13</sup>	Onset (days); Positive Dechallenge; Event Recovery, Daily Dose (mg)	Outcomes
4	suicidality, new onset	suicide attempt, overdose	affective disorder, anxiety, depression, personality change	9793207; 60M	Direct; USA; HCP	unk; NA; unk ;unk	HO,LT
<p><i>Patient with no prior psychiatric history (no medications, hospitalizations, or suicide attempts) presented to inpatient psychiatric facility after an overdose (250 pills of tramadol) with no identifiable trigger (no alcohol or illicit drug contribution, or psychosocial stressors). Patient reports starting using Chantix for smoking cessation approximately 2-3 weeks ago, and had discontinued medication 2-3 days prior to overdose/suicide attempt after noticing a change in mood and personality, including depression and anxiety.</i></p>							
5	suicidality, new onset	suicide attempt	depression, feeling guilty	9210428; 23M	Expedited (15-Day); foreign; HCP	35; unk; unk ;unk	DS,HO,LT
<p><i>Patient attempted suicide, was feeling guilty and had depression since an unspecified date in 2013. He associated his feelings of extreme depression and guilt about "not working hard enough" in his job to around the time he started varenicline tartrate. He jumped 90 feet off a building, received multiple fractures including an unstable lumbar fracture, and was admitted to intensive care. Prior to starting varenicline tartrate the patient had no suicidal thoughts.</i></p>							
6	suicidality, new onset	completed suicide	anger, asthenia, decreased appetite, depressed mood, depression, negative thoughts, sleep disorder	9667868; 51M	Expedited (15-Day); foreign; HCP	unk; NA; no ;2	DE,OT
<p><i>Patient began Chantix on 3/14/13 and committed suicide in (b) (6). He left a letter describing increasing depression, reduced appetite, no happiness, trouble sleeping, lack of energy and "felt that it was no way out of it" after starting Chantix. His wife had remarked that he had changed, with more anger, after he started using Chantix.</i></p>							
7	suicidality, worsening	suicide attempt, suicidal ideation,	depression	10068819; 39M	Expedited (15-Day); USA; HCP	25; yes; yes ;2	HO,OT
<p><i>While on Chantix, he attempted suicide by hanging himself. Patient was treated in a mental health unit for 4 days. Medical history included depression, described as "did not feel right" since an unknown date in 2014, bipolar disorder, and gastroesophageal reflux disease. No concomitant medications.</i></p>							
8	psychosis- mania, worsening	delusion of grandeur, schizophreniform disorder, paranoia	aphagia, disturbance in attention, insomnia, mood swings, palpitations	10066963; 32M	Expedited (15-Day); foreign; CON	10; yes; yes ;unk	OT



Case Index	Event Category	Key Event	Other Events	Case ID; Age/Sex	Report Type; Country; Reporter <sup>13</sup>	Onset (days); Positive Dechallenge; Event Recovery, Daily Dose (mg)	Outcomes
10 days after starting Chantix, patient experienced delusions, mixed and paranoid state, lasting about a week. He stated that thankfully he was able to recognize the signs that something was wrong and cope to some degree. He suffered from a drug induced psychosis 12 years ago, but was never asked about mental health problems when prescribed Chantix. He stated that "this medication was not appropriate for people who had suffered from mental health problems in the past."							
9	other, new onset	disturbance in attention, feeling abnormal, memory impairment,	impaired work ability, performance status decreased	10182580; 53F	Direct; USA; CON	unk; unk; unk ;2	OT
Patient "had no issues until started taking Chantix." He had problems with memory, forgetfulness, and his attention was "not what it should be." Patient feels like he is "losing his mind, putting his job in jeopardy am not performing to the best of his ability."							
10	other, worsening	depression	none	10243650; 58M	Non- Expedited; USA; CON	35; unk; unk ;unk	OT
The consumer reported that depression got worse about a month after starting varenicline tartrate. Relevant laboratory data was none. Relevant medical history included mild depression. He stopped varenicline in response to the worsening depression.							
11	other, worsening	anxiety, depression, disturbance in attention, memory impairment	aphasia, dysarthria, impaired work ability, speech disorder	10037625; 34F	Direct; USA; HCP	21; no; yes ;unk	OT
Patient began on Chantix in December of 2013 for smoking cessation. Patient had previously tried the medication with success and had no adverse effects from that medication the first time she used it. After about 3 weeks, the medication severely worsened her anxiety and depression and worsened her concentration and short term memory. Additionally, she had trouble with her speech (example: slowing and slurring of her speech as well as difficulty finding the words for what she is trying to say). Patient has been unable to work due to these symptoms. As of March 2014, the patient reports that her mood and anxiety have improved. However, she is still suffering from short term memory loss, difficulty with speech, as well as concentration issues. The Chantix was stopped when the symptoms first appeared.							
12	psychosis- mania, worsening	hallucination, auditory	abnormal behavior, confusional state, depression, flat affect, psychiatric symptom	9434498; 54M	Direct; USA; HCP	unk; yes; yes ;unk	HO

Case Index	Event Category	Key Event	Other Events	Case ID; Age/Sex	Report Type; Country; Reporter <sup>13</sup>	Onset (days); Positive Dechallenge; Event Recovery, Daily Dose (mg)	Outcomes
<p>Patient was taking varenicline and experienced bizarre behavior after 80 days of therapy. He made a statement that he had killed someone and that he was also experiencing voices to commit suicide. He also had a "flat affect" with limited speech. He was hospitalized for psychiatric symptoms. His pre-existing depression and chronic paranoid schizophrenia were noted to be stable prior for 6 months prior to starting varenicline. The caregiver had felt that the patient had decompensated after varenicline was started. At one month follow up notes indicate patient denied having active and passive suicidal thoughts.</p>							
13	other, new onset	affect lability, depressed mood, depression	no others	9998990; 30M	Direct; USA; CON	11; yes; yes ;2	DS
<p>Approximately 11 days after starting Chantix, patient "began to feel sad." He subsequently experienced a "swing of emotions" over the next days ranging from happiness to depression to anger and stopped taking Chantix.</p>							
14	other, new onset	euphoric mood, affect lability, thinking abnormal, anxiety, mental status changes, depression, crying, confusional state, irritability, disturbance in attention	none	9647953; 24F	Direct; USA; CON	14; yes; yes ;2	DS,OT
<p>Patient experienced "abnormal changes in mental health" described as "depression, anxiety, irritability, extreme confusion, trouble concentration, emotional instability, and unwanted sexual thoughts" after a couple of weeks of Chantix. She experienced "unbearable anxiety and confusion" and failed exams after studying. She was "extremely mean to her boyfriend," "treated him badly," and "said things that she would normally never say to him."</p>							
15	other, worsening	depression, feeling abnormal	anger, suicidal ideation	9657214; 53M	Non- Expedited; USA; CON	3; yes; yes ;unk	OT
<p>Patient experienced anger, depression, and suicidal thoughts 3 days after starting Chantix. He quit Chantix "for a while," restarted and "the same thing happened again." Patient reports that he "never felt like that in his life." Relevant medical history included depression, for which he was treated with sertraline and a neck injury, for which he was scheduled for surgery. Chantix was stopped and action with sertraline was unknown.</p>							

Case Index	Event Category	Key Event	Other Events	Case ID; Age/Sex	Report Type; Country; Reporter <sup>13</sup>	Onset (days); Positive Dechallenge; Event Recovery, Daily Dose (mg)	Outcomes
16	aggression, worsening	aggression, anger	abnormal behavior, depression, feeling abnormal, loss of employment, nightmare, suicidal behavior	9667718; 62M	Expedited (15-Day); USA; HCP	3; unk; unk ;unk	OT
<p><i>Patient's wife noticed a severe change in behavior within the first 11 days of starting Chantix. Patient "felt weird," had nightmares, and was depressed. He "cursed people out at his job, lost his job, and starting talking about leaving this earth." He later put a knife to his wife's throat and police were notified. Chantix was immediately discontinued. His wife reports that "her husband had been a hardworking, honest, and dependable employee all his life." His co-workers thought he "went crazy". They had been married 30 years, and nothing like this had ever happened before. Relevant concomitant medications included fluoxetine for an unspecified indication and for which he was "presumably doing well."</i></p>							
17	aggression; new onset	aggression, verbal abuse, anger	personality change, irritability, educational problem, suicidal ideation, apathy, abnormal dreams, obsessive thoughts, verbal abuse, partner stress, decreased interest, anger	9711960; 28M	Direct; USA; CON	unk; no; no ;2	DS
<p><i>Consumer reports that since taking Chantix, he has become somebody "mean spirited, aggressive and a flat out monster to those who love me." He never had these problems before taking Chantix and used to be as "happy as could be." The drug turned him into a "verbally abusive boyfriend to the love of my life and he lost her because of this." He further describes the events as "extreme aggression, severe headaches, blind rage (Going from [a scale of] 1 to 100 with my anger in a matter of seconds), irritation, hate for people in general, lack of motivation, restless legs, vivid dreams" and suicidal thoughts.</i></p>							
18	aggression; new onset	homicidal ideation	abnormal behavior, hyperacusis, insomnia, nightmare, parosmia, personality change	9731985; 46F	Expedited (15-Day); foreign; HCP	60; yes; yes ;unk	OT
<p><i>A 46-year-old female experienced a personality change (described as "aggression") approximately 2 months after starting Chantix. She reported a nightmare about "strangling her mother's throat" also described as "an attempt to kill her mother." She did not have those symptoms in the first 2 months of Chantix and did not have any history of psychiatric disease. She was also sensitive to noise and smell and could not sleep. She completed the course of Chantix and continuously abstained from smoking regardless of the described events. Patient reported that she still had a "feeling of aggression and used abusive language to her mother" after finishing varenicline treatment.</i></p>							

Case Index	Event Category	Key Event	Other Events	Case ID; Age/Sex	Report Type; Country; Reporter <sup>13</sup>	Onset (days); Positive Dechallenge; Event Recovery, Daily Dose (mg)	Outcomes
19	psychosis- mania; new onset	hallucination, visual, mania, paranoia	anxiety, paranoia	9970724; 26F	Direct; USA; CON	2; no; no ;1	OT
<i>Consumer reports "feeling on edge" 2 days after starting Chantix, which quickly progressed to hallucinations, paranoia (described as "fangs on my small child and demon like things in the shadows"), and "full blown anxiety attacks." She reports that she "never had anxiety issues before this" and "coworkers and family said I was manic."</i>							
20	other; new onset	affect lability, anger, anxiety, emotional disorder	anger	9416696; 32M	Expedited (15-Day); foreign; CON	1; yes; yes ;unk	OT
<i>A 32-year-old male experienced anger, mixed range of emotions, and emotional instability while on Chantix in 2011, received Chantix again in 2013 as he was "desperate to stop smoking." After the first dose, he became anxious and angry and "felt uncontrolled." Chantix was discontinued and symptoms resolved.</i>							

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/s/  
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MARTIN L POLLOCK  
09/05/2014

SARA L CAMILLI  
09/05/2014

SCOTT E PROESTEL  
09/07/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Provision of Pharmacovigilance Data**

**Date:** May 16, 2014

**Reviewer:** Sara Camilli, PharmD, BCPS, Safety Evaluator Team Leader  
Division of Pharmacovigilance II (DPV II)

**Director:** Scott Proestel, MD, Director  
DPV II

**Product Name:** Chantix (varenicline tartrate)

**Subject:** Neuropsychiatric Events Crude Counts 2008-2013

**Application Type/Number:** NDA 21928

**Applicant/Sponsor:** Pfizer, Inc.

**OSE RCM #:** 2014-749

## 1 INTRODUCTION

This document provides crude counts of FDA Adverse Event Reporting System (FAERS) data for domestic varenicline and neuropsychiatric event reports for 2008-2013 in support of a Center Director Briefing.

On April 8, 2014, Pfizer submitted a supplement that proposes removal of the Boxed Warning for neuropsychiatric events for varenicline. To address this proposal, a Center Director Briefing will be held on May 22, 2014, and an Advisory Committee meeting is planned for the fall of 2014. The Division of Epidemiology consulted the Division of Pharmacovigilance II (DPV II) to provide updated crude counts of FAERS data since the last review, completed in 2008, for the Center Director Briefing.

Neuropsychiatric adverse events were initially added to the Adverse Reaction section of the product labeling in November 2007. Subsequently, it was elevated to a Warning in January 2008 and a Boxed Warning in July 2009, consistent with recommendations of two DPV II reviews.<sup>a b</sup> A Risk Evaluation and Mitigation Strategy (REMS) and postmarketing study requirement for a large clinical safety trial of neuropsychiatric events were issued in May 2008. Results of the postmarketing study are expected in 2017.

## 2 METHODS AND MATERIALS

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1.<sup>c</sup>

<b>Table 1. FAERS Search Strategy</b>	
Date of search	May 13, 2014
Time period of search	Event Date OR Initial Receive Date: 01/01/2008 – 12/31/2013
Active Ingredient	Varenicline, varenicline tartrate
Search Terms	See Appendix A
Country (derived)	US

## 3 DATA

The FAERS database received 48,200 domestic adverse event reports for varenicline from January 1, 2008, through December 31, 2013. Of the 48,200 reports, 17,739 (37%) were neuropsychiatric adverse event reports, of which 572 (3%) reported a fatal outcome.

<sup>a</sup> Pollock M, Mosholder A. Psychiatric events (including suicides) associated with varenicline and bupropion. December 8, 2008. OSE RCM# 2008-1291.

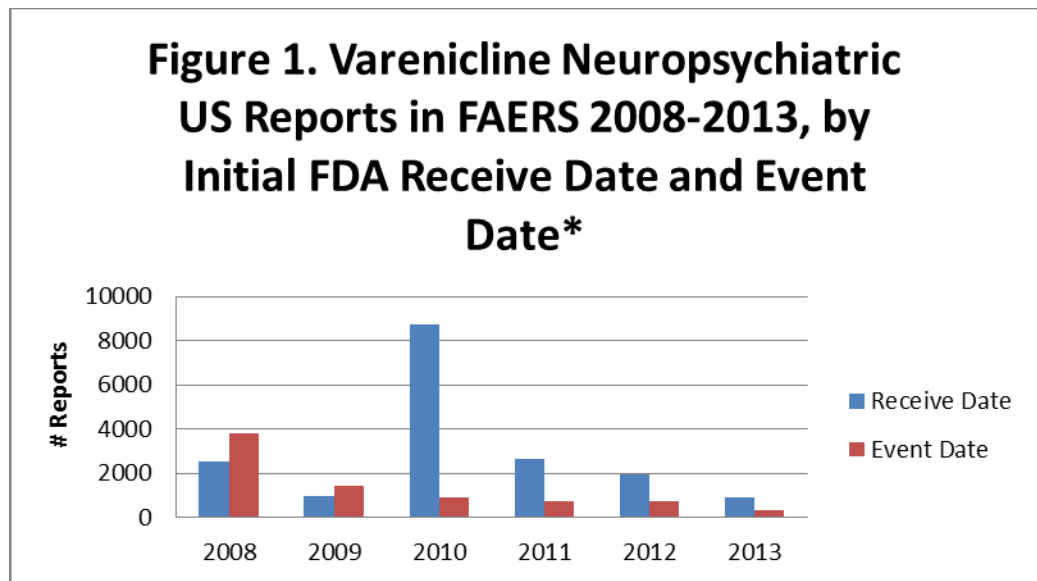
<sup>b</sup> Pollock M, Mosholder A. Suicidality associated with varenicline, bupropion, and nicotine transdermal patch. July 16, 2008. OSE RCM #2007-2425.

<sup>c</sup> FAERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population. FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

Table 2 and Figures 1 - 3 provide crude counts of domestic neuropsychiatric adverse event reports in FAERS for 2008 through 2013. The data is provided by initial receive date and event date. FDA received a bolus of reports in 2010 that corrected a submission error of Pfizer's periodic reports. Therefore, looking at trends in the reports by event date may provide a more accurate picture of the adverse events over time. A limitation of trending reports by event date is that all reports will not be captured, as event date may not be reported or may be prior to the time period of interest. Of the 17,739 neuropsychiatric reports received from 2008 to 2013 for varenicline, 12,176 (69%) provided an event date, of which 4,420 (36%) occurred prior to 2008.

The FAERS data shows that FDA continues to receive reports of neuropsychiatric events associated with varenicline. Numbers of reports for all types of neuropsychiatric events declined from 2008 through 2013. Figure 4 provides crude level data for fatal neuropsychiatric events, which has also declined over time.

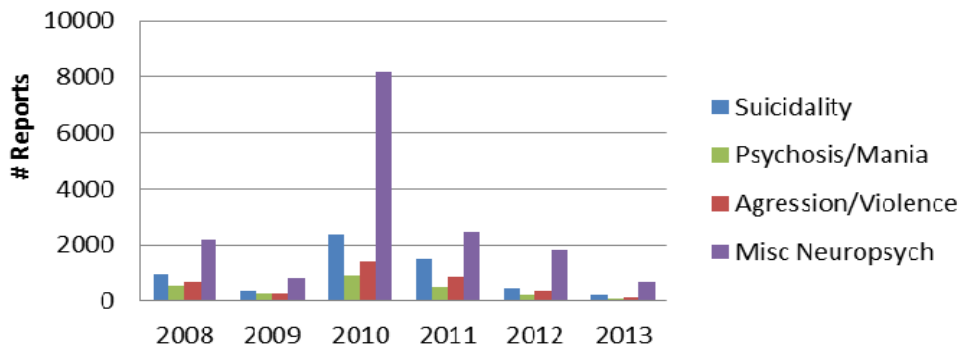
Table 2. FAERS Crude Counts for Varenicline and Neuropsychiatric Events U.S. Reports 2008-2013										
Year	FDA Initial Receive Date					Event Date				
	All	Suicid- ality	Psychosis/ Mania	Aggression/ Violence	Misc. Neuropsych	All	Suicid- ality	Psychosis/ Mania	Aggression/ Violence	Misc. Neuropsych
2008	2555	969	524	682	2210	3798	1634	584	917	3272
2009	989	376	246	288	792	1424	791	291	430	1180
2010	8716	2353	892	1426	8189	899	222	157	169	767
2011	2637	1497	481	868	2442	737	129	97	149	622
2012	1946	453	239	369	1820	755	87	81	119	673
2013	896	208	75	144	680	364	57	28	68	316
Total	17739	5856	2457	3777	16133	7977	2920	1238	1852	6830



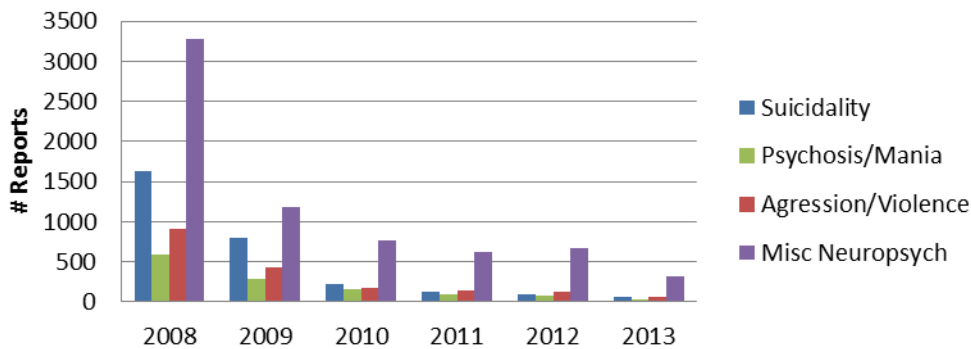
\*Of the 17,739 neuropsychiatric reports received from 2008 to 2013 for varenicline, 12,176 (69%) provided an event date, of which 4,420 (36%) occurred prior to 2008.



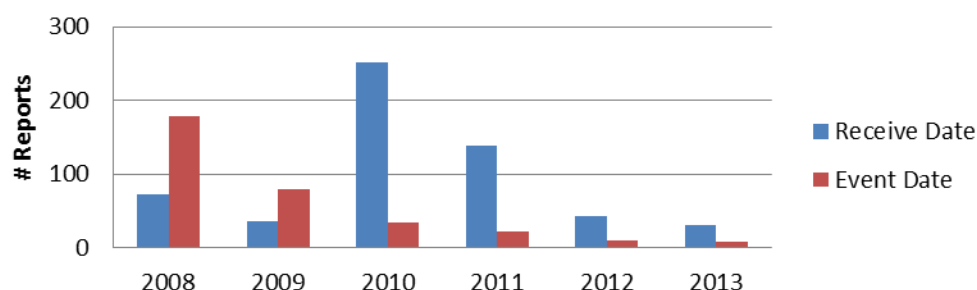
**Figure 2. Varenicline Neuropsychiatric US Reports in FAERS 2008-2013, by Initial FDA Receive Date**



**Figure 3. Varenicline Neuropsychiatric US Reports in FAERS 2008-2013, by Event Date**



**Figure 4. Fatal Varenicline Neuropsychiatric US Reports in FAERS 2008-2013, by Initial FDA Receive Date and Event Date\***



\*Of the 572 fatal neuropsychiatric reports received from 2008 to 2013 for varenicline, 462 (81%) provided an event date, of which 131 (28%) occurred prior to 2008.

#### 4 APPENDIX A

Table 3. MedDRA Preferred Terms (PTs) for Select Categories of Neuropsychiatric Events			
Suicidality	Psychosis Mania	Aggression/Violent Behavior	Miscellaneous
Suicidal and self-injurious behavior NEC (HLGT)	Mania	Aggression	Abnormal behavior
Depression suicidal	Paranoia	Belligerence	Amnestic symptoms (HLT)
Gun shot wound	Catatonia	Anger	Confusional state
Intentional drug misuse	Hypomania	Hostility	Mood alterations with depressive symptoms (HLT)
Overdose	Schizotypal personality disorder	Physical assault	Depression
	Schizophrenia and other psychotic disorders (HLGT)	Sexual abuse	Major depression
	Delusion symptoms (HLT)	Homicide	Disorientation
	Perception disturbances (HLT)	Imprisonment	Emotional disorder
	Bipolar disorders (HLT)	Homicidal ideation	Emotional distress
	Schizoid personality disorder		Feeling abnormal
	Paranoid personality disorder		Mood altered

<b>Table 3. MedDRA Preferred Terms (PTs) for Select Categories of Neuropsychiatric Events</b>			
<b>Suicidality</b>	<b>Psychosis Mania</b>	<b>Aggression/Violent Behavior</b>	<b>Miscellaneous</b>
			Mood swings
			Personality change
			Thinking abnormal
			Anxiety disorders with symptoms (HLGT)
			Trichotillomania
			Sleep disorder
			Tic disorders (HLT)

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/s/  
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SARA L CAMILLI  
05/16/2014

SCOTT E PROESTEL  
05/16/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: 7/16/08

To: Bob Rappaport M.D., Director  
Division of Anesthesia, Analgesia, and Rheumatology Products  
(DAARP)

Thru: Ann McMahon, M.D., M.S., Acting Director  
Lauren Lee, Pharm.D., Team Leader  
Division of Adverse Event Analysis II

Solomon Iyasu, M.D., Director  
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From: Martin Pollock, Pharm.D., Safety Evaluator  
Joann H. Lee, Pharm.D., Safety Evaluator  
Division of Adverse Event Analysis II

Andrew Mosholder, M.D., Epidemiologist  
Laura Governale, Pharm.D., MBA, Drug Use Analyst Team Leader  
Division of Epidemiology

Subject: Suicidality

Drug Name(s): varenicline; bupropion; nicotine transdermal patch

Application Type/Number: 021928 (varenicline; Chantix); 020711 (bupropion; Zyban)<sup>1</sup>;  
020076 (nicotine transdermal patch, Habitrol<sup>2</sup>)

Applicant/sponsor: Pfizer (varenicline); GSK (bupropion; Zyban); Novartis (nicotine  
transdermal)

OSE RCM #: 2007-2425

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<sup>1</sup>Also available as generic (Buproban, Teva Pharmaceuticals).

<sup>2</sup>Other brands include Nicoderm CQ (020165; Sanofi-Aventis) and Nicotrol (020536 Pfizer).

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## EXECUTIVE SUMMARY

Varenicline (Chantix; Pfizer; NDA 21928) is a smoking cessation drug approved on 5/10/06. This consult is in response to a request from the Division of Analgesics, Anesthetics, and Rheumatology Drug Products (DAARP) for a review of all suicide-related events associated with varenicline from the Adverse Event Reporting System (AERS) database. This consult contains (1) a review of AERS postmarketing reports of suicidal events for varenicline and two other smoking cessation drugs, bupropion and nicotine transdermal patch, (2) a review of suicidal events from varenicline clinical trials and a review of Pfizer's analysis of postmarketing adverse events, Pfizer's medical literature review of smoking cessation and suicidality and disproportionality analysis, and (3) an analysis of drug utilization patterns for varenicline, bupropion, and transdermal nicotine transdermal patches. Bupropion and transdermal nicotine were used as comparator drugs in this review because they are the currently approved alternate smoking cessation products.

## AERS CASES

Three smoking cessation products (varenicline, bupropion, and transdermal nicotine) were evaluated for a possible association of their use to suicide related events. As of 11/27/07, the AERS database contained 262 reports (for all outcomes) of suicidal ideation and suicide (attempted/completed) involving varenicline (n=153), bupropion (n=75), and nicotine transdermal patch<sup>3</sup> (n=34). Varenicline had a higher proportion of cases for suicidal ideation (76%) vs. bupropion (61%) or nicotine (47%) and a lower proportion of suicide (attempt and completed) or other self injurious behavior (24%) than the other drugs (bupropion 39%; nicotine 53%). Depression was the most commonly co-reported psychiatric event in all the cases (varenicline 45%, bupropion 35%, nicotine 15%).

Among the cases reporting gender (252/262, 96%) there was approximately a 2 to 1 ratio of females to males reported with varenicline and transdermal nicotine; there was a smaller gender difference with bupropion (females 53% vs. males 47%). The median patient age was similar for all 3 drugs (varenicline 45 years, bupropion 41 years, and nicotine 41.5 years).

In almost all cases (95 to 98%) for the 3 smoking cessation drugs, the recommended dose was used (when known) indicating that under or overdosing was an unlikely explanation for the reported events. The median time to event onset was less than two weeks for all three drugs. In most of the cases for varenicline (72%) and bupropion (89%) and in half for nicotine (50%), the suicide related events occurred while the patients were on smoking cessation therapy compared to the event occurrence after discontinuation (varenicline 12%, bupropion 7%, nicotine 6% ).

Suicidal events were reported in patients with (varenicline 50%, bupropion 24%, and nicotine 65%) or without (varenicline 26%, bupropion 32%, and nicotine 3%.) psychiatric history. Bupropion case series had the most cases with no concomitant psychiatric medications reported (33%) followed by varenicline (21%) and nicotine (9%). The most common concomitant medication was antidepressants for all three smoking cessation drugs.

A similar proportion of cases for varenicline (35%) and bupropion (33%) reported a positive dechallenge (24% positive dechallenge for nicotine); positive *rechallenges* were reported in fewer cases for varenicline (n=1) and bupropion (n=2) and in none for nicotine. Most (varenicline, 96%; bupropion 79%) or all (nicotine) of the cases had a serious outcome. For all drugs,

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<sup>3</sup>Nicotine transdermal patch will hereafter be referred to as 'nicotine.'

hospitalization (varenicline 12%, bupropion 28%, nicotine 38%) and death (varenicline 12%, bupropion 13%, nicotine 15%) were reported. Completed suicides with varenicline had more contributing factors (28%) than nicotine (20%) or bupropion (10%). However, information on such contributing factors was unknown more often with bupropion and nicotine (both 80%) compared to varenicline (67%). In almost three-quarters (13/18) of the nicotine cases of suicide (completed or attempt), due to lack of information in the reports, it was not able to be determined if the patient was using the patch for a smoking cessation indication. This made it difficult to assess any association with the *therapeutic* use of the patch with completed or attempted suicides.

In conclusion, The AERS data suggest a possible association between suicidal events and the use of varenicline and bupropion, given that there were postmarketing cases of positive dechallenge, close temporal relationship between the event and drug use, and the occurrence of suicidal events in patients without any psychiatric history. Suicide ideation cases for transdermal nicotine products also suggest a possible drug to event association; however, a further review of all nicotine formulations would be needed to confirm these findings. In a majority of Nicotine Suicide attempt/completed cases drug/association not clear due to lack of info; also other drug formulation;

## **REVIEW OF CLINICAL TRIALS, SPONSOR SUBMISSIONS, AND THE LITERATURE**

On 10-5-07, Pfizer submitted a pooled analysis of suicidal adverse events from their clinical trial data for varenicline. Among 4906 varenicline-treated patients they identified 4 suicidal events, including one completed suicide following discontinuation of varenicline, and among 1487 placebo-treated patients they identified 2 suicidal events. It is not clear if an expanded search for suicidal events in the clinical trial database would yield a sufficient number of events for a meaningful analysis, but the existing clinical trial data can neither rule in nor rule out an association of such events with varenicline treatment. It should be borne in mind that patients with active psychiatric disorders were by and large excluded from the clinical studies.

Data mining using FDA's WebVDME application on AERS data for 12 suicidal or self-injury preferred terms returned a lower bound confidence interval estimate (EB05) equal to or greater than 2.0 times the expected for two preferred terms: suicidal behavior (EB05 = 2.8) and suicidal ideation (EB05 = 3.3). Similarly, for Zyban, suicide attempt (EB05 = 2.0), and suicidal ideation (EB05 = 2.8) had EB05 scores  $\geq 2.0$ ; however, none of the 12 suicide/self-injury preferred terms were associated with an EB05  $\geq 2.0$  for any trade name nicotine product.

Reporting rates of suicidal events (i.e., reports of suicidal events in AERS compared to prescriptions dispensed) during the first two calendar years of marketing has been higher for varenicline than for Zyban, and considerably higher for varenicline than for transdermal nicotine. There is some evidence for stimulated reporting, beginning in September of 2007, when reports for varenicline increased considerably while prescriptions were stable or slightly declining.

Pfizer provided a literature review and an expert opinion report by Dr. John Hughes from the University of Vermont. Key findings from the literature may be summarized as follows: (1) there is an association between smoking and suicidal behavior; (2) smoking cessation is associated with depressed mood, but an association with frank major depressive disorder has not been as well documented; (3) it has not been documented that smoking cessation per se is a risk factor for suicide; and (4) major psychiatric disorders are associated with smoking.

With respect to prospects for observational data on the association of varenicline with suicidal and other psychiatric events, we have learned that the Department of Veteran's Affairs has initiated a retrospective analysis of roughly 27,000 varenicline users, 100,000 nicotine replacement users, and 12,000 bupropion users. The preliminary data reportedly suggest a slightly



higher rate of hospitalization for psychosis among varenicline users, but no conclusions can be drawn at this stage.

## DRUG UTILIZATION PATTERNS

Wholesale distribution patterns for the smoking deterrents class USC 69000 revealed that the volume of these products sold (in tablets, individual patches, gums, etc.) nearly doubled between years 2006 and 2007 from 369 million to 684 million extended units, respectively. Varenicline was the most widely distributed product during year 2007, accounting for over 60% of the market, followed by nicotine products (gums, transdermal patches, etc.) with nearly 32%. Bupropion products accounted for less than 2% of the market in year 2007.

In terms of dispensed prescriptions, varenicline accounted for nearly 94% of the “smoking deterrents” market followed by nicotine transdermal patch products at 3.5% of the market during year 2007. Bupropion products accounted for less than 1% of the market. Approximately a third of varenicline prescriptions were dispensed to patients who were on prior therapy with varenicline in the previous six months. Of those, nearly 14% of dispensed prescriptions for varenicline were preceded by a bupropion product.

For bupropion products, approximately 25% were dispensed to patients who were on prior therapy with Zyban<sup>®</sup> or Buproban<sup>®</sup> in the previous six months. Of those, approximately 81% of dispensed prescriptions for bupropion were preceded by varenicline. This indicates a low rate of persistency for varenicline.

Concurrency analysis revealed that nearly 40% of patients taking varenicline were on concurrent therapy with a product in the antidepressant-antipsychotic-anxiolytic market during year 2007. Similar results were found for patients taking Zyban<sup>®</sup> or Buproban<sup>®</sup>.

## OVERALL CONCLUSION

- In AERS, 262 cases of suicidal-related events for the smoking cessation drugs were found (varenicline, n=153; bupropion, n=75; transdermal nicotine, n=34). Varenicline had a higher proportion of cases for suicidal ideation (76%) vs. bupropion (61%) or nicotine (47%) and a lower proportion of suicide (attempt and completed) or other self injurious behavior (24%) than the other drugs (bupropion 39%; transdermal nicotine 53%).
- Varenicline had the largest proportion of reports (24%) in which it was explicitly stated that the suicidal event(s) were a first-time significant behavior change from the past, followed by bupropion (15%) and nicotine (none). Varenicline cases had the most reports that described pre-existing disease worsening (17%) compared to nicotine (12%) and bupropion (8%); depression was the most common pre-existing psychiatric condition that worsened for all 3 drugs.
- In most of the cases for varenicline (72%) and bupropion (89%) and in half for nicotine (50%), the suicide related events occurred while the patients were on smoking cessation therapy compared to the event occurrence *after discontinuation* (varenicline 12%, bupropion 7%, nicotine 6% ).
- AERS data suggest a possible association between suicidal events and the use of varenicline and bupropion, given that there were postmarketing cases of positive dechallenge/rechallenge, close temporal relationship between the event and drug use, and the occurrence of suicidal events in patients without any psychiatric history.

- Although suicide ideation cases for transdermal nicotine suggest a possible drug to event association, a further review of all nicotine formulations may be warranted.
- Clinical trial data for varenicline is not adequate to either rule in or rule out an association between suicidal behaviors and varenicline treatment, owing to the small number of such events reported in the trials.
- Reporting of suicidal events proportional to prescriptions dispensed during the first two calendar years of marketing has been higher for varenicline than for bupropion, and considerably higher for varenicline than for transdermal nicotine. Given that there was a substantial increase in the number of such reports for varenicline during the final months of 2007 that was not accompanied by an increase in prescriptions, it seems likely that stimulated reporting accounts for this recent increase in the number of reports of suicidal events. Accordingly, comparisons to reporting rates for other products must be interpreted with caution.
- An observational study of the occurrence of psychiatric events with varenicline treatment may provide useful data, and efforts are underway to conduct such a study through the Department of Veterans Affairs. Reporting of suicidal events proportional to prescriptions dispensed during the first two calendar years of marketing has been higher for varenicline than for Zyban and considerably higher for varenicline than for transdermal nicotine.
- Wholesale distribution patterns and dispensed prescriptions for the smoking deterrents class USC 69000 revealed that during year 2007 varenicline was the most widely distributed product accounting for over 60% in sales volume and nearly 94% in dispensed prescriptions, followed distantly by nicotine products (gums, transdermal patches, etc.) with nearly 32% in sales and 3.5% in dispensed prescriptions. Bupropion products accounted for less than 2% of sales and less than 1% of dispensed prescriptions in year 2007.
- During year 2007, only a third of varenicline prescriptions were categorized as continuing therapy, whereas only a quarter were categorized as continuing therapy for bupropion products. Although we could not accurately measure the use of OTC nicotine transdermal products, there appears to be a high degree of switching within the class of smoking cessation products.
- Concurrency analysis revealed that nearly 40% of patients taking varenicline were on concurrent therapy with a product in the antidepressant-antipsychotic-anxiolytic market during year 2007. Similar results were found for patients taking Zyban<sup>®</sup> or Bupropion<sup>®</sup>.
- The seriousness of the suicidality related AERS reports for varenicline, its higher reporting rate compared to bupropion, and its foreseeable widespread future use in patients who want to quit smoking necessitate the regulatory actions mentioned below. These actions can help provide for increased awareness so that practitioners can better manage suicidal-related events in patients taking varenicline or bupropion.

## RECOMMENDATIONS

### Varenicline

- a) The existing Neuropsychiatric WARNINGS, in the labeling, should be elevated to a **Box Warning**.<sup>4</sup>
- b) The current wording in the labeling ‘suicidal ideation and suicidal behavior,’ should be revised to ‘suicidal ideation and suicidal behavior *including suicide attempt and completed suicide.*’
- c) The labeling should include that “*in most cases, neuropsychiatric symptoms developed during Chantix treatment, but in others, symptoms developed following withdrawal of Chantix therapy.*”<sup>5</sup>
- d) We recommend a clinical trial to assess the safety of varenicline use and to determine the incidence of neuropsychiatric symptoms with varenicline, especially in patients with pre-existing psychiatric disorders. Ideally, such a trial would include a comparison to other smoking cessation therapies. There will of course be many design issues to consider, including sample size, subject selection, protections for the subjects, and comparison groups; however, a complete discussion would be beyond the scope of the present review.

### Bupropion

For Zyban labeling,<sup>6</sup> we recommend the following wording for the existing Box warning:

*Depression, including suicidal ideation, completed suicide and suicide attempt have been reported in patients taking Zyban for smoking cessation. These event have occurred in patients:*

- a) With and without pre-existing psychiatric disease; some have had their psychiatric illness worsened.*
- b) In most cases, these events developed during Zyban treatment, but in others, these events developed following withdrawal of Zyban therapy.*

### Nicotine

The findings in this case series support a further review of the other nicotine dosage formulations for suicidal-related events.

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<sup>4</sup>Criteria for a Black Box Warning: Special problems, particularly those that may lead to *death or serious injury*, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. 21 CFR part 201.57(e) Warnings. April 1, 2002.

<sup>5</sup>As per Healthcare Advisory, February, 2008.

<sup>6</sup>This wording also needs to be incorporated into labeling for *other* bupropion products (i.e. Wellbutrin, generics).

# 1 BACKGROUND

## 1.1 INTRODUCTION

Varenicline (Chantix; Pfizer; NDA 21928) is a smoking cessation drug approved on 5/10/06. This consult is in response to a request from the Division of Analgesics, Anesthetics, and Rheumatology Drug Products (DAARP) for a review of all suicide-related events associated with varenicline from the Adverse Event Reporting System (AERS) database. This consult contains (1) a review of AERS postmarketing reports of suicidal events for varenicline in addition to two other smoking cessation drugs, bupropion and nicotine transdermal patch,<sup>7</sup> (2) an epidemiology review of suicidal events from varenicline clinical trials, Pfizer's analysis of varenicline postmarketing adverse events, Pfizer's medical literature review of smoking cessation and suicidality, disproportionality analysis, and (3) an analysis of drug utilization patterns for varenicline, bupropion, and transdermal nicotine transdermal patches.

## 1.2 REGULATORY HISTORY

Varenicline was approved on 5/10/06<sup>8</sup> (NDA 21928; Pfizer) and is indicated as an aid to smoking cessation treatment.<sup>9</sup> Varenicline (Champix) was approved in Europe on 9/26/06. In May 2007, the EMEA informed FDA that they were investigating a signal of suicidal-related events with varenicline and had asked Pfizer to submit a postmarketing suicidal-event analysis. An AERS database search on 6/26/07 retrieved 26 non-fatal suicidal-related reports.<sup>10,11</sup>

On 9/3/07, a celebrity rock-musician Carter Albrecht, who was taking varenicline for smoking cessation for one week, was shot to death by a neighbor after he exhibited violent-bizarre behavior toward his girlfriend. Albrecht's girlfriend was widely quoted in the press saying that she believed Albrecht's unusual behavioral change was due to varenicline. While the final disposition of this case is not known, alcohol was reported to be a confounding factor.<sup>12</sup> Subsequently, additional anecdotal reports of varenicline and psychiatric-related events such as depression and suicidality started to appear in the media.<sup>13</sup>

In September 2007, DAARP submitted a request to Pfizer for an analysis of postmarketing reports of suicidality and aggressive and irrational behavior associated with varenicline. In October 2007, the FDA received two submissions from Pfizer, one for suicidality (n=102; See **3.2 EPIDEMIOLOGY**) and one for aggression/hallucinations/irrational behavior (n=525). After an initial review of this data, it was decided that there appeared to be a signal for behavioral changes with varenicline and that the public should be informed. An Early Communication was issued in

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<sup>7</sup>Bupropion (Zyban; 020711; GlaxoSmithKline) was approved 5/14/97; nicotine transdermal patch (Habitrol; Novartis; NDA 020076) was approved on 11/27/91

<sup>8</sup>Chantix was first distributed to U.S. wholesalers the week of 7/10/06 (personal communication with Pfizer Drug Information Department, 7/13/07).

<sup>9</sup>Chantix product labeling; INDICATIONS AND USAGE; Pfizer Labs, N.Y., N.Y. January 2008.

<sup>10</sup>Pollock M.; Varenicline and suicidality; Analysis of AERS reports for EMEA. Presented at video-con on 7/17/07. AIMS# 2007-1441.

<sup>11</sup>Chantix U.S. labeling, as initially approved listed *suicidal ideation*. The European labeling, on initial approval did not list any suicidal-related events. Champix Product Information; (<http://www.emea.europa.eu/humandocs/PDFs/EPAR/champix/H-699-PI-en.pdf>)

<sup>12</sup>Eiserer, T. Autopsy: Carter Albrecht intoxicated 3 times the legal limit. *The Dallas Morning News* 10/22/07. <http://www.dallasnews.com/sharedcontent/dws/news/localnews/stories/102207dnmetalbrecht.197ab4f40.html>

<sup>13</sup>PeoplesPharmacy.com; Can Chantix cause depression? 9/17/07; Scary side effects of Chantix 10/17/07; Stop-smoking drug linked to suicidal thoughts 12/10/07.

November 2007.<sup>14</sup> At the same time, the **ADVERSE REACTIONS** section of the varenicline labeling was revised to include reports of changes in behavior including suicidal events.

The EMEA issued a press release in December 2007 regarding the occurrence of depression and suicidality (ideation and attempt).<sup>15</sup> In February 2008, the FDA issued a Public Health Advisory.<sup>16</sup> This was accompanied by a second varenicline labeling change under **WARNINGS (See 1.3 Product Labeling)** which described neuropsychiatric symptoms. It was also mentioned that the events have occurred in patients who were smoking or who had quit; some patients experienced worsening of their pre-existing psychiatric history.

On 4/14/08, a Regulatory Briefing with the Center Director concerning varenicline and psychiatric-related events was held. The benefits of varenicline to help patients achieve cessation from smoking vs. the risks of psychiatric adverse events were discussed.

On 5/16/08, DAARP informed Pfizer to submit a proposed Risk Evaluation and Mitigation Strategy (REMS) for neuropsychiatric events.<sup>17</sup> The components of the REMS requested by FDA are a medication guide (approved on 5/16/08), communication plan to healthcare providers, and postmarketing clinical studies 'to assess the known serious risk of neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions.'<sup>17</sup>

### 1.3 PHARMACOLOGY AND DOSAGE AND ADMINISTRATION

#### Varenicline

Varenicline is a partial agonist<sup>18</sup> for the neuronal nicotinic acetylcholine receptor subtype  $\alpha_4\beta_2$  which is known to be involved with nicotine addiction. Varenicline-stimulation of the  $\alpha_4\beta_2$  receptor maintains dopamine levels in the brain which can prevent nicotine craving and withdrawal symptoms in the patient who is trying to quit smoking. Varenicline also makes smoking undesirable because by occupying the  $\alpha_4\beta_2$  receptor, varenicline also acts as an *antagonist* which can prevent nicotine from achieving any receptor activation.<sup>18</sup>

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<sup>14</sup>Early Communication About an Ongoing Safety Review: Varenicline (marketed as Chantix); 11/20/07; [http://www.fda.gov/cder/drug/early\\_comm/varenicline.htm](http://www.fda.gov/cder/drug/early_comm/varenicline.htm)

<sup>15</sup>Press Release: European Medicines Agency concludes new advice to doctors and patients for Champix needed. 12/14/076. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/champix/59551607en.pdf>. There was also a labeling change made.

<sup>16</sup>FDA Public Health Advisory: Important Information on Chantix (varenicline) 2/1/08; <http://www.fda.gov/cder/drug/infopage/varenicline/default.htm>

<sup>17</sup>Rappaport B (DAARP) NDA supplement (21-928/S-008) approval letter sent to 5/16/08 to Pfizer Inc. The actual details of the clinical trials are still to be determined by DAARP

<sup>18</sup>A partial agonist is an agonist that has a smaller maximal effect at full receptor occupancy than does the full agonist (i.e. nicotine). Varenicline has about 43% receptor efficacy compared with nicotine. Rollema J, Coe JM, Chambers LK, Hurst SR et al. Rationale, pharmacology and clinical efficacy of partial agonists of  $\alpha_4\beta_2$  nACh receptors for smoking cessation. *Trends Pharmacol. Sci.* 2007;28:316-325.

## Dosing and administration is as follows:

### Usual Dosage for Adults

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Patients should be provided with appropriate educational materials and counseling to support the quit attempt.

The patient should set a date to stop smoking. CHANTIX dosing should start one week before this date.

CHANTIX should be taken after eating and with a full glass of water.

The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – End of treatment:	1 mg twice daily

Patients who cannot tolerate adverse effects of CHANTIX may have the dose lowered temporarily or permanently.

Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence.

Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

### **Bupropion (Zyban; Buproban [generic])**

The anti-smoking effect of bupropion might be accomplished through its weak inhibition of dopamine and norepinephrine reuptake as well as antagonism of the nicotinic acetylcholine receptor.<sup>19</sup> The exact mechanism of action in smoking cessation is believed to be complex and not known.<sup>19,20</sup>

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<sup>19</sup>Foley KF, DeSanty KP, Kast RE. Bupropion: pharmacology and therapeutic applications. *Future Drugs Ltd* 2006;6:1249-1265.

<sup>20</sup>Zyban labeling; Clinical Pharmacology; GlaxoSmithKline, Research Triangle Park, N.C.; September, 2006.

Dosing and administration is as follows:

### **DOSAGE AND ADMINISTRATION**

**Usual Dosage for Adults:** The recommended and maximum dose of ZYBAN is 300 mg/day, given as 150 mg twice daily. Dosing should begin at 150 mg/day given every day for the first 3 days, followed by a dose increase for most patients to the recommended usual dose of 300 mg/day. There should be an interval of at least 8 hours between successive doses. Doses above 300 mg/day should not be used (see WARNINGS). ZYBAN should be swallowed whole and not crushed, divided, or chewed. Treatment with ZYBAN should be initiated **while the patient is still smoking**, since approximately 1 week of treatment is required to achieve

steady-state blood levels of bupropion. Patients should set a “target quit date” within the first 2 weeks of treatment with ZYBAN, generally in the second week. Treatment with ZYBAN should be continued for 7 to 12 weeks; longer treatment should be guided by the relative benefits and risks for individual patients. If a patient has not made significant progress towards abstinence by the seventh week of therapy with ZYBAN, it is unlikely that he or she will quit during that attempt, and treatment should probably be discontinued. Conversely, a patient who successfully quits after 7 to 12 weeks of treatment should be considered for ongoing therapy with ZYBAN. Dose tapering of ZYBAN is not required when discontinuing treatment. It is important that patients continue to receive counseling and support throughout treatment with ZYBAN, and for a period of time thereafter.

**Maintenance:** Nicotine dependence is a chronic condition. Some patients may need continuous treatment. Systematic evaluation of ZYBAN 300 mg/day for maintenance therapy demonstrated that treatment for up to 6 months was efficacious. Whether to continue treatment with ZYBAN for periods longer than 12 weeks for smoking cessation must be determined for individual patients.

### **Nicotine transdermal**

Nicotine transdermal drug products act as a nicotinic acetylcholine receptors to mimic or replace the effects of nicotine from tobacco.<sup>21</sup> Nicotine patches are marketed in 7, 14, and 21 mg strengths.

Dosing and administration:

If patient smokes >10 cigarettes/day: 21 mg/24 hr for 6-8 weeks; decrease to 14 mg/24 hr for 2-4 weeks; then decrease to 7 mg/24hr for 2-4 weeks.

If patient smokes ≤10- cigarettes/day: 14 mg/24 hr for 6 weeks; decrease to 7 mg/24 hr for 2-4 weeks.

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<sup>21</sup>Benowitz NL. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. *Clin. Pharmacol. Therapeut.* 2008;83:531-541.

## 1.4 PRODUCT LABELING FOR SUICIDAL-RELATED EVENTS

### Varenicline

Initial labeling (approved 5/10/06) listed suicidal ideation (from clinical trials) as *rare* under PSYCHIATRIC DISORDERS.

Suicidal ideation and suicide was added in November, 2007<sup>14</sup> under **ADVERSE REACTIONS, Post-Marketing Experience:**

There have been reports of depressed mood, agitation, changes in behavior, suicidal ideation and suicide in patients attempting to quit smoking while taking Chantix. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. The role of Chantix in these reports is not known.

The labeling of psychiatric events was expanded and upgraded to a WARNING in February 2008.<sup>16</sup>

### WARNINGS

#### Neuropsychiatric Symptoms

Serious neuropsychiatric symptoms have occurred in patients being treated with CHANTIX. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking; however, some of these symptoms have occurred in patients who continued to smoke. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, suicidal ideation and suicidal behavior. These symptoms, as well as worsening of pre-existing psychiatric illness, have been reported in patients attempting to quit smoking while taking CHANTIX in the post-marketing experience. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established. Patients attempting to quit smoking with CHANTIX and their families and caregivers should be alerted about the need to monitor for these symptoms and to report such symptoms immediately to the patient's healthcare provider.

### Bupropion (Zyban)

Zyban labeling (August 2007) has a boxed warning for suicidality as follows: .



#### Suicidality and Antidepressant Drugs

Although ZYBAN is not indicated for treatment of depression, it contains the same active ingredient as the antidepressant medications WELLBUTRIN®, WELLBUTRIN SR®, and WELLBUTRIN XL®. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of ZYBAN or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ZYBAN is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

Zyban labeling also has a **PRECAUTION** concerning suicidal ideation, depression and nicotine withdrawal:

***Depression and Nicotine Withdrawal:*** Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in patients undergoing a smoking cessation attempt (see **WARNINGS: Clinical Worsening and Suicide Risk**).

Zyban and Wellbutrin labeling has “suicidal ideation occurring as *infrequent*.” under the **ADVERSE REACTIONS** section.

#### Nicotine transdermal patch

There is no mention of any safety information related to suicidality.<sup>22</sup>

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<sup>22</sup>Nicotine transdermal system stop smoking aid (patch). PDR for nonprescription drugs, dietary supplements, and herbs; 29<sup>th</sup> ed; Thomson Healthcare Inc., Montvale, NJ; 2007. The only safety-related information that is psychiatric is under **When using this product**: ‘if you have vivid dreams or other sleep disturbances remove this patch at bedtime.’ A similar statement is repeated under **Directions**.

## 2 METHODS

### 2.1 AERS SELECTION OF CASES

#### 2.1.1 Varenicline

On 11/27/07, the AERS database was searched for the suspect drug, varenicline, for US reports<sup>23</sup> from the time of drug approval with the suicidal terms listed in Table 2.1.1.1.<sup>24</sup> Another AERS search was conducted with the same drug and time period criteria as above for *all events*.

**Table 2.1.1.1. MedDRA terms for suicidal-related events.**

MedDRA Term	Hierarchy
Suicidal and self-injurious behaviour	HGLT <sup>25</sup>
Multiple drug overdose	PT
Depression suicidal	PT
Gun shot wound	PT
Intentional misuse	PT
Overdose	PT

The reports were further classified into two groups:

(1) **‘Suicidal ideation’**; there was no intent of patient-harm reported; events were *Suicidal ideation, Self-injurious ideation, or Suicidal depression*

or

(2) **‘Suicide (attempt or completed) and other self-injury’**; intent of patient harm reported; events were *Completed suicide, Attempted suicide, Intentional self-injury, Self-injurious behavior, Suicidal behavior, Multiple drug overdose, Gun shot wound, Intentional misuse, or Overdose*.

For all cases, particular attention was focused on identifying those reports where it was stated that the behavior change associated with the suicidality was a significant change from the past, i.e. prior to taking varenicline

(1) the suicidal event(s) were a first-time occurrence for the patient, i.e. the patient had no history or remembrance of ever having experienced such events or

<sup>23</sup>Reports were also captured for NULL country. From previous experience with varenicline, it has been found that most of the NULL country reports were from the U.S. Any foreign cases were eliminated in the individual case review.

<sup>24</sup>These were the same suicidal-related terms used in a previous OSE review for psychiatric events associated with drugs indicated to treat Attention Deficit Hyperactivity Disorder (Galperin K, Phelan K. Psychiatric events associated with drugs to treat ADHD: Review postmarketing safety data. Division of Drug Risk Evaluation; Office of Drug Safety; D050243; March 3, 2006).

<sup>25</sup>Contains one HLT (Suicidal and self-injurious behaviour) which has the following PT's: Completed suicide, Intentional self-injury, Self-injurious behaviour, Self-injurious ideation, Suicidal behaviour, Suicidal ideation and Suicide attempt.

(2) the patient did have a history of a psychiatric disease, but it was being adequately treated and or was felt to be under control. After taking varenicline, the pre-existing psychiatric disease worsened.

### **2.1.2 Bupropion**

On 11/27/07, the AERS database was searched for the suspect drug, bupropion, for all US<sup>23</sup> reports from the time of drug approval for all events.

The reports were then extracted from AERS and further processed in Microsoft Office® Access.<sup>26</sup> Reports were retrieved that met the following criteria:

- (1) trade name of Zyban or (2) indication of smoking cessation
- and
- (3) one or more of the suicidal-related terms in Table 2.1.1.1

The reports were classified as to their events, as mentioned for varenicline in 2.1.1. Reports were identified with significant behavioral change from the past, as explained for varenicline in 2.1.1.

Although Zyban is marketed exclusively for smoking cessation, a patient could also be taking a generic or Wellbutrin for his/her antismoking therapy. Therefore, this broad search strategy was adopted to capture as many reports as possible.

### **2.1.3 Nicotine transdermal patch**

On 11/27/07, the AERS database was searched for the suspect drug, nicotine, for all US reports<sup>23</sup> from the time of drug approval for all events. The reports were then extracted from AERS and further processed in Microsoft Office® Access.<sup>26,26</sup> Reports were retrieved that met the following criteria:

- (1) trade name of Habitrol, Nicoderm, Nicoderm CQ, or Prostep<sup>27</sup> or (2) ‘topical,’ ‘transdermal’ or ‘patch’ as descriptor
- and
- (2) one or more of the suicidal-related terms in Table 2.1.1.1

The reports were classified as to their events, as mentioned for varenicline in 2.1.1. Reports were identified with significant behavioral change from the past, as explained for varenicline in 2.1.1.

A broad search strategy was employed because of the variability of how the nicotine transdermal therapy was mentioned in the report. No single parameter (trade name, dose form or administration route) could encompass all the reports.

## **2.2 REVIEW OF CLINICAL TRIALS, SPONSOR SUBMISSIONS, AND THE LITERATURE**

The following sources of information were reviewed: (1) the sponsor’s analysis of suicidal events in varenicline clinical trials, submitted 10-5-07; (2) the sponsor’s analysis of postmarketing

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<sup>26</sup>The extract is a file that contains 206 different fields from the MedWatch (or electronically submitted) report. The relevant fields examined included all suspect drugs, drug name (verbatim and trade), total dose, indication, all reactions and narrative..

<sup>27</sup>Prostep report were only included where it could be determined that the route as transdermal because Prostep was also available as an oral formulation.

reports of suicidal events with varenicline treatment; (3) the sponsor's analysis for the EMEA on disproportionality in reporting of suicidal events, supplemented by a similar analysis using FDA's WebVDME data mining application; (4) the sponsor's review of the literature on smoking and suicidal events. In addition, sources of observational data on this issue that are available to FDA were explored.

Reporting rates for suicidal events were calculated for the first two calendar years each drug product was marketed. The count of suicidal event reports was determined by the AERS case review of reports for each drug product; cases with an FDA receipt date falling during the first two calendar years that the drug was on the market were included in the numerator. (For this purpose, we ignored the fact that the cut-off date for the varenicline case series was approximately one month before the end of 2007.) The denominator was the number of prescriptions dispensed for the product according to Verispan, LLC: Vector One®: National (VONA) (see below) during the first two calendar years the drug was on the market. We used prescriptions for Zyban as a proxy for bupropion's use in smoking cessation, although other bupropion products may have been used for this indication. For varenicline we also examined reporting rates by month, comparing prescriptions dispensed to the number of AERS reports of suicidal events received during each month of 2007. To determine the extent of retrospective reporting, we compared the event date (after verification of the date of the event by hands-on review) to the date the report was received.

### **2.3 DRUG USAGE PATTERNS**

Drug utilization patterns for varenicline (Chantix®), bupropion (Zyban®, Buproban®), and transdermal nicotine patches were examined for years 1991 through 2007 using the following data resources:

The IMS Health, IMS National Sales Perspectives™ was used to gain a comprehensive view of the sale of all products in the USC5 Class 69000 "Smoking Deterrents". Total dispensed prescriptions was obtained from the Verispan, LLC: Vector One®: National (VONA) for calendar years 1991 through 2007, and total projected number of patients was obtained from the Verispan, LLC: Vector One®: Total Patient Tracker (TPT) for years 2002 to 2007, and also cumulatively from year 2002 to 2007. Concurrent psychotropic drug use (Antidepressants-Antipsychotics-Anxiolytics) with Chantix® or bupropion (Buproban®, Zyban®) products were also examined using the Verispan, Vector One®: Concurrence (VOCON) tool. Detailed description of the methods used and the databases are described in Appendix 5 and 6.

## **3 RESULTS**

### **3.1 AERS CASES**

#### **3.1.1 Varenicline**

The AERS search retrieved a total of 3,017 varenicline reports for all events. There were 172 unique cases coded with one or more of the suicidal-related events. Nineteen of the 172 cases were excluded as shown in Table 3.1.1.1.

**Table 3.1.1.1 Varenicline excluded cases**

Reason for exclusion	N
Misuse with no intent to harm	9
Patient reduced dose to mitigate non-psychiatric-adverse event	5
Patient did not comply with dosing regimen	3
Therapeutic use without physician's authorization	1
Event occurred before varenicline administration	4
Patient did not experience event	2
Experienced by friend	1
Heard of event experienced by another party	1
'Symptoms felt like overdose' <sup>28</sup> ; dose was as per recommended	1
Patient retracted experiencing event	1
Overdose without clear documentation of intentional self-harm	1
Event occurred long after use of varenicline	1
Total	19

Demographics and other selected information is given for the 153 cases in Table 3.1.1.2.

**Table 3.1.1.2 Demographics and other parameters of varenicline AERS suicidal adverse event cases (n=153)**

Parameter	Suicidal ideation(N=116) ) <sup>29,30</sup>	Suicide (attempt or completed) and other self-injury (N=37) <sup>30,31</sup>
<b>Age (years)</b>	n=106 mean 44.5; median 44.5; range 20-83	n=27 mean 46.3; median 47.4; range 22-72
<b>Sex</b>	n=115	n=34
Male	30	17
Female	85	17
Event onset while taking varenicline	Yes 87; no 15; unknown 14	Yes 23; no 3; unknown 11
Event onset while taking varenicline (days)	n=55; mean 22.0; median 8 ; range 1-150	n=16; mean 19.6; median 14; range 2-90
Event onset after varenicline discontinued (days)	n=10; mean 4.1; median 3; range 1-7	n=3; mean 53.7; median 17; range 2-124 <sup>32</sup>
Varenicline discontinued	Yes 96; no 10; unknown 10	Yes 18; no 9; unknown 10

<sup>28</sup>“Nausea, vomiting, headache, was almost comatose, felt shaky, had chills and fever, was sensitive to light and her equilibrium was off.”

<sup>29</sup>‘Suicidal ideation’ includes cases where no there was no intent of patient-harm reported reported. This group includes events coded with the following PT's: *Suicidal ideation, Self-injurious ideation or Suicidal depression*.

<sup>30</sup>If for any particular parameter, the total number of cases (usually the number that were evaluable) is not specified, this means it was the same as the total of particular event group (**Suicidal ideation, n=116; Suicide [attempt or completed] and other self-injury, n=37**).

<sup>31</sup>Suicide (attempt or completed) and other self-injury ideation’ includes cases where an intent of patient-harm was reported. This group includes events coded with the following PT's: *Completed suicide, Attempted suicide, Intentional self-injury, Self-injurious behavior, Suicidal behavior, Multiple drug overdose, Gun shot wound, Intentional misuse, and Overdose*.

<sup>32</sup>A 29-year-old female (no prior psychiatric history; no concomitant medication) had taken varenicline during the first-half of 2007; therapy ended 5/31/07. In June, 2007 and continuing through the summer, the patient had behavior changes, crying, rage, anxiety, loss of interest in activities, and depression; At the end of the summer, the patient

<b>Outcome</b> <sup>33</sup>		
Serious	110	37
Death	0	19
Hospitalization	12	7
Life-threatening	26	5
Disability	6	3
Required intervention <sup>34</sup>	6	0
Other	92	20
Non-serious	6	0
Treatment/intervention for event	24	8
<b>Recovery</b>	n=85	n=10
Yes	45	6
Partial	16	1
No	24	3
<b>Dose (at time of event)</b>	n=82	n=16
Within recommended <sup>35</sup>	78	15
Lower than recommended	3	1
Higher than recommended	1	0
<b>Suicidal-related event</b>	Suicidal ideation 110 Self-injurious ideation 6	Completed suicide 18 Suicide attempt 15 <sup>36</sup> Intentional-self injury 3 Overdose 1 <sup>37</sup>
<b>Other co-reported psychiatric events</b> <sup>33</sup>		
No	2	12
Yes	114	25
Depression	60	9
Anxiety	26	4
Abnormal dreams	19	0
Crying	19	4
Feeling abnormal	19	2
Insomnia	16	0
Anger	13	1
Nightmare	13	0

became depressed and in September had suicidal ideation which lasted 10 days and culminated in a suicide attempt (hanging) on 10/2/08.

<sup>33</sup>Not mutually exclusive

<sup>34</sup>All had at least one other outcome

<sup>35</sup>Recommended per labeling

<sup>36</sup>One case involved a gun shot wound (recovered) that appeared to be a suicide attempt, even though not coded as such.

<sup>37</sup>45-year-old female who after starting varenicline 'lost her mind' and overdosed on insulin, metformin, a bottle of fexofenadine and a bottle of 'sleeping pills'

<b>Psychiatric-related history</b> <sup>33</sup>	n=92	n=25
No	29	11
Yes	63	14
Depression	37	8
Bipolar/mood disorder/mania	20	3
Anxiety	11	2
Suicide attempt	7	0
Post traumatic stress syndrome	5	1
Psychiatric hospitalization	5	0
Suicide ideation	3	0
Psychosis	2	0
Self-mutilation	0	2
Aggression/delusion	1	1
Family history of depression and/or suicide	5	0
Personality disorder	3	0
Panic disorder	3	0
Other	6 <sup>38</sup>	1 (anorexia nervosa)
<b>Concomitant medications (psychiatric-related and/or labeled for suicidality)</b> <sup>33</sup>	n=72	n=20
No	23	9
Yes	49	11
Antidepressant	38	10
Anxiolytic	24	8
Mood stabilizer/anticonvulsant	19	1
Antipsychotic	18	4
Antiepileptic	4	0
Stimulant	2	0
Sedative hypnotic	2	1
Other	3 <sup>39</sup>	0

<sup>38</sup>One each of: homicidal ideation, seasonal affective disorder, delusions, attention deficit disorder, psychiatric disorder NOS (was taking fluoxetine and alprazolam), pre-menstrual dysphoric disorder.

<sup>39</sup>unnamed drug to treat Post-traumatic stress disorder (n=1); drugs labeled for suicidality: anti-obesity (sibutramine; n=1) and a biologic response modifier (glatiramer acetate; 'Copaxone'; n=1)

<b>Smoking information</b>		
Smoking status at event	n=30	n=8
Quit	19	5
Smoking	11	3
Smoking duration (years)	n=15; median 24.3	n=6; median 23.5
Number of packs per day	n=13; median 1	n=2; 1.5 and 'heavy smoker'
Previous attempts to quit	n=16; no (2); yes (14)	n=4; no (1); yes (3)_
Previous antismoking therapy	n=10	n=3
Varenicline	3	1
NRT gum	2	2
NRT patch	5	1
NRT inhaler	1	0
Zyban	1	0
<b>Substance use/abuse</b>		
Concomitant use/abuse	n=25 no (15) yes (10); alcohol (9); marijuana(1)	n=11 no (4) yes (7); alcohol (6); methamphetamine (1)
Prior history of use/abuse	n=29 no (14) yes (15); alcohol (12); marijuana (2); other substances (3)	n=9 no (3) yes (6); alcohol (6)
<b>Dechallenge</b>	n=58	n=7 <sup>40</sup>
Positive	49	5
Negative	9	2
Rechallenge, positive	1	0
<b>FDA received year</b>		
2006	1	0
2007	115	37
<b>Report type</b>		
Direct	55	14
Expedited	61	23
<b>Reporter</b>		
Healthcare professional	19	21
Consumer (or representative)	96	15
Other (FDA district inspector)	1	1

### Significant change in behavior from past

There were 63/153 (41%) cases where it was stated that after taking varenicline, a significant change from the past had occurred. In 37 of the 63 cases this was a first time experience and in the remaining 26 cases there was a worsening of pre-existing psychiatric disease (which the reporter had previously felt to be stable). Examples of such experiences (excerpt from report) were:

<sup>40</sup>For non-fatal



## First time experience

‘she was a different person’; ‘I knew this was not normally me’; ‘this erratic behavior was very uncommon for him’; patient took on a different personality that was not known before.’

## Worsening of pre-existing disease

‘my depression was under control until I began varenicline’ ‘depression had worsened’; ‘bipolar was under control until I started taking Chantix’; ‘been taking 37.5 mg Paxil since 1998 with no problems.’

A selection (n=38)<sup>41</sup> of the 63 cases is listed in Appendix 1.

### 3.1.2 Bupropion

The AERS search retrieved a total of 23,038 bupropion reports for all adverse events. There were 5,019 reports that mentioned bupropion being used for smoking cessation. Of the 5,019 reports, there were 125 unique cases that reported one or more suicidal-related events. Fifty of the 125 cases were excluded as shown in Table 3.1.2.1.

**Table 3.1.2.1. Bupropion excluded cases**

Reason for exclusion	N
Overdose without clear documentation of intentional self-harm	27
Not prescribed for smoking cessation or indication not specified	8
No psychiatric adverse event in report	8
Duplicate	2
Event occurred long after use of bupropion	2
Conflicting information of relationship between bupropion exposure and event onset	1
Illegible	1
Bupropion clinical trial (treatment blinded)	1
Total	50

Demographics and other selected information for the 75 evaluable cases are presented in Table 3.1.2.1

<sup>41</sup>Because varenicline had many more such reports than the other drugs (Bupropion, n=17, nicotine, n=5), it was decided to present a portion (60%; n=38) of the varenicline reports. The 38 reports in Appendix 1 are of a similar proportion of the full population, such that there are 22 (58%) for first time behavior changes and 16 (42%) for disease worsening.

**Table 3.1.2.1 Demographics and other parameters of bupropion AERS suicidal adverse event cases (n=75)**

Parameter	Suicidal ideation (N=46) <sup>42,43</sup>	Suicide (attempt or completed) and other self-injury (N=29) <sup>43,44,42</sup>
<b>Age</b> (years)	n=33 Mean 44.8; median 46 ; range 26-70	n=24 Mean 34.8; median 35; range 15 <sup>45</sup> -51
<b>Sex</b>	n=43	n=29
Male	17	17
Female	26	12
Event onset while taking bupropion	Yes 43; no 3; unknown 3	Yes 24; no 2
Event onset while taking bupropion (days)	n=25; mean 34.5; median 12.5; range 1-334	n=15; mean 44; median 14; range 4- 365
Event onset after bupropion discontinued (days)	7 days (n=1); unknown 2	14 days (n=1); unknown 1
Bupropion discontinued	Yes 37; no 3; unknown 6	Yes 14; no 4; unknown 11
<b>Outcome</b> <sup>46</sup>	n=46	n=29
Serious	30	29
Death	0	10
Disability	3	2
Hospitalization	9	12
Life-threatening	10	6
Required intervention	1	1
Other	11	7
Non-Serious	16	0
Treatment/intervention for event	15	11
<b>Recovery</b>	n=30	n=8
Yes	21	6
Partial	4	1
No	5	1
<b>Dose</b> (at time of event)	n=26	n=14
Within recommended	25	14

<sup>42</sup>'Suicidal ideation' includes cases where there was no intent of patient-harm reported. This group includes events coded with the following PT's: *Suicidal ideation, Self-injurious ideation or Suicidal depression*.

<sup>43</sup>If for any particular parameter, the total number of cases (usually the number that were evaluable) is not specified, this means it was the same as the total of particular event group (**Suicidal ideation, n=46; Suicide [attempt or completed] and other self-injury, n=29**).

<sup>44</sup>'Suicide (attempt or completed) and other self-injury' includes cases where an intent of patient-harm was reported. This group includes events coded with the following PT's: *Completed suicide, Attempted suicide, Intentional self-injury, Self-injurious behavior, Suicidal behavior, Multiple drug overdose, Gun shot wound, Intentional misuse, and Overdose*.

<sup>45</sup>There were two pediatric patients (both 15 years-old).

<sup>46</sup>Not mutually exclusive

Higher than recommended	1	0
<b>Suicidal-related event</b>	Suicidal ideation 45 Suicidal depression 1	Completed suicide 10 Suicide attempt 15 <sup>47</sup> Intentional self-injury 2 Overdose 2 <sup>48</sup>
<b>Other co-reported psychiatric events</b> <sup>46</sup>		
No	22	16
Yes	24	13
Depression	20	6
Insomnia	4	2
Paranoia	4	0
Aggression	3	1
Anxiety	3	1
Agitation	2	2
Homicidal ideation	2	1
Mania	2	2
Psychosis	2	1
Abnormal behavior	0	1
<b>Psychiatric-related history</b> <sup>46</sup>	n=28	n=14
No	16	8
Yes	12 <sup>49</sup>	6
Depression	7	5
Mania/other mood disorder	6	0
Psychotic disorder	2	0
Anxiety	1	0
Past psychiatric hospitalization	1	1
Past suicide attempt	1	2
<b>Concomitant medications</b> (psychiatric-related and or labeled for suicidality) <sup>46</sup>		
No	n=28 19	n=11 6
Yes	9	5
Antidepressant	4	3
Mood stabilizer/anticonvulsant	4	1
Anxiolytic	4	3
Antipsychotic	2	1
Sedative	1	0
Other <sup>50</sup>	2	1
<b>Smoking information</b>		

<sup>47</sup>Two of the suicide attempts also involved overdoses.

<sup>48</sup>One patient became depressed and took a full bottle of sleeping pills; another patient overdosed on 40 bupropion 150 mg SR tablets.

<sup>49</sup> Other/unspecified (n=4)

<sup>50</sup>For Suicidal ideation isotretinoin (n=1) and hypericum (n=1); for suicide (attempt/completed) and other self-injury 'tranquilizer' NOS (n=1).

Smoking status at event	n=6	n=5
Quit	1	1
Smoking	5	4
How long smoking?	n=5; median 11 years	n=0
How many packs per day	n=8; median 1	n=0
Previous attempts to quit?	n=0	n=3; yes
Previous antismoking therapy	n=0	n=3; bupropion 2; nicotine replacement
<b>Substance use/abuse</b>		
Concomitant use	Yes (1) marijuana	Yes (9) (alcohol 7; marijuana & stimulants 1; PCP 1)
Prior history of abuse	Yes (2) alcohol	Yes (3) alcohol
<b>Dechallenge</b>	n=25	n=6
Positive	21	4
Negative	4	2
Rechallenge, positive	2	0
<b>FDA received year</b>		
1997-1999	18	8
2000-2004	16	12
2005-2007	12	9
<b>Report type</b>		
Expedited	11	18
Periodic	19	3
Direct	16	8
<b>Reporter</b>		
Healthcare professional	13	14
Consumer (or representative)	32	13
Attorney	1	0
Other	0	2

### Significant change in behavior from past

There were 17/75 (23%) cases where it was stated that after taking bupropion, a significant change from the past had occurred. In 11 of the 17 cases this was a first time experience and in the remaining 6 cases there was a worsening of pre-existing psychiatric disease (which the reporter had previously felt to be stable). Examples of such experiences (excerpt from report) were:

#### First time experience

‘It was not her usual state of being’; ‘never had been depressed in his life until taking Wellbutrin. It cost me the life I once knew.’

#### Worsening of pre-existing disease

‘worsening of depression’; ‘reactivation of manic depression.’

The 17 cases are listed in Appendix 2.

### 3.1.3. Nicotine Transdermal

The AERS search retrieved a total of 39,869 nicotine reports for all adverse events. There were 28,192 reports that mentioned use of a nicotine transdermal patch. Of the 28192 reports, there were 500 that reported one or more suicidal-related events; 466 of the 500 reports were excluded as shown in Table 3.1.3.1.

#### Table 3.1.3.1 Nicotine excluded cases

Reasons for exclusion	N
Unrelated to suicidal events	456 <sup>51</sup>
Duplicate reports	10
Total	466

Demographics and other selected information for the 34 evaluable cases are presented in Table 3.1.3.2

**Table 3.1.3.2 Demographics and other parameters of nicotine transdermal AERS suicidal adverse event cases (n=34)**

Parameter	Suicidal Ideation (N=16) <sup>52,53</sup>	Suicide (attempt or completed) and other self-injury (N=18) <sup>53,54</sup>
Age (years)	n=15 mean 43.2; median 42; range 22-68	n=17 mean 44.0; median 41; range 15 <sup>55</sup> -72
Sex	n=15	n=16
Male	6	6
Female	9	10
Event onset while taking nicotine patch	Yes 14; no 2	Yes 3; no 0; unknown 15
Event onset while using nicotine patch (days)	n=9; mean 14; median 6; range 2-60	n=0
Event onset after nicotine discontinued (days)	n=1; mean 1; median 1	n=0
Nicotine patch discontinued	Yes 14; no 1; unknown 1	Yes 3; no 1; unknown 14
<b>Outcome</b> <sup>56</sup>		
Serious	16	18
Death	0	5
Hospitalization	2	11
Life Threatening	0	2
Disability	0	0
Required Intervention	0	4
Other	14	8
Treatment/intervention for event	2	10
<b>Recovery</b>	n=11	n=9
Yes	9	9

<sup>51</sup>Overdose cases with no mention of suicidality.

<sup>52</sup>'Suicidal ideation' includes cases where there was no intent of patient-harm reported. This group includes events coded with the following PT's: *Suicidal ideation, Self-injurious ideation or Suicidal depression*.

<sup>53</sup>If for any particular parameter, the total number of cases (usually the number that were evaluable) is not specified, this means it was the same as the total of particular event group (**Suicidal ideation, n=16; Suicide [attempt or completed] and other self-injury, n=18**).

<sup>54</sup>'Suicide (attempt or completed) and other self-injury ideation' includes cases where an intent of patient-harm was reported. This group includes events coded with the following PT's: *Completed suicide, Attempted suicide, Intentional self-injury, Self-injurious behavior, Suicidal behavior, Multiple drug overdose, Gun shot wound, Intentional misuse, and Overdose*.

<sup>55</sup>These was one pediatric patient (15 years-old).

<sup>56</sup>Not mutually exclusive

No	2	0
<b>Dose</b> (at time of event) <sup>56</sup>	n=15	n=6
Within recommended	15	5
Lower than recommended	0	0
Higher than recommended	0	1
<b>Suicidal-related event</b>	Suicidal ideation 10 Self-injurious ideation 6 <sup>57</sup>	Completed suicide 5 Suicide attempt 13
<b>Other co-reported psychiatric events</b> <sup>56</sup>		
No	n=10	n=16
Yes	n=6	n=2
Depression	3	2
Anxiety	2	1
Psychosis	1	0
Aggression	2	0
Crying	4	0
<b>Contributing Psychiatric History</b> <sup>56</sup>		
No	n=9	n=14
Yes	1	0
Depression	8	14
Schizophrenia	5	9
Psychosis	2	1
Psychiatric disorder	0	1
Suicidal ideation	3	4
	0	1
<b>Concomitant medications</b> (psychiatric-related and/or labeled for suicidality) <sup>56</sup>	n=12	n=6
No	3	0
Yes	9	6
Antidepressant	7	5
Mood stabilizer/anticonvulsant	0	0
Benzodiazepine	1	0
Antianxiety	2	1
Antipsychotic	8	2
Sedative	0	0
Stimulant	1	2
<b>Smoking information</b>		
Smoking status at event	n=5	n=1
Quit	3	1
Smoking	2	0
How long smoking?	n=6; median 29 years	n=2; median 47 years
How many packs per day?	n=6; median 1	n=2; median 2
Previous attempts to quit	n=3; yes 3	0
Previous antismoking drug therapy	n=3; 1=NRT gum; 1=Zyban; 1=unknown	0
Reported		
<b>Substance use/abuse</b>	n=1	n=2
Concomitant use/abuse	Yes (1) alcohol	Yes (2) alcohol (1); stimulant (1)

<sup>57</sup>One case involved a self-injurious behavior (e.g. pen marking on wrist to be cut)

Prior history of use/abuse	0	Yes (1) alcohol
<b>Dechallenge</b>	n=9	n=1
Positive	7	1
Negative	2	0
<b>Rechallenge, positive</b>	n=0	n=0
<b>FDA received year</b>		
1992-1994	0	4
1995-1999	2	12
2000-2004	6	1
2005-2007	8	1
<b>Report type</b>		
Expedited (15-day)	14	16
Published literature	0	12 <sup>58</sup>
Periodic	2	1
Direct	0	1
<b>Reporter type</b>		
Health Care Professional	2	16
Patient or consumer on patients' behalf	13	2
Other	1	0

### Significant change in behavior from past

There were 4 (12%) of the cases where it was stated that after taking transdermal nicotine, a significant change from the past had occurred. In all of these cases, there was a worsening of pre-existing psychiatric disease (which the reporter had previously felt to be stable). An example of such an experience was:

'aggravated the pre-existing depression.'

The 4 cases are listed in Appendix 3.

## 3.2 REVIEW OF CLINICAL TRIALS, SPONSOR SUBMISSIONS, AND THE LITERATURE

### 3.2.1 Pfizer's Submissions

#### 3.2.1.1 Analysis of suicidality from original Chantix clinical trials

Pfizer submitted on 10-5-07 a pooled analysis of data from Phase II-III clinical trials of varenicline for smoking cessation. The sponsor searched for MedDRA preferred terms indicating adverse events of a suicidal nature.<sup>59</sup> The search was limited to "treatment emergent" events arising during treatment and for up to 7 days afterwards. The results are shown in the table below.

<sup>58</sup>Eight cases were from one published literature report. This was a prospective post-marketing surveillance project from U.S. poison centers, identified nine adults who intentionally overdosed on transdermal nicotine patches in 1997 by applying more than one patch simultaneously (coded as suicide attempt or completed suicide). Woolf A, Burkhart K, Caraccio T, Litovitz T. Self-poisoning among adults using multiple transdermal nicotine patches. *J. Toxicol. Clin. Toxicol.* 1996;34:691-698. The remaining four cases were each from a separate published literature report.

<sup>59</sup>Terms comprising the MedDRA Suicide/self-injury SMQ: completed suicide, depression suicidal, intentional overdose, intentional self-injury, multiple drug overdose intentional, poisoning deliberate, self-injurious behavior, self-mutilation, self-injurious ideation, suicidal behavior, suicidal ideation, and suicide attempt.

Table 3.3.1.1 a: Sponsor's 10-5-07 Update

Treatment group	Varenicline	Placebo	Bupropion	Nicotine patch
Total subjects*	5,071	1,655	795	370
Total patient-years	1,192	355	130	60
Number of suicidal events	1**	1***	0	0
*These are pooled data from various trials with different comparator treatments, so the N's don't match **Intentional overdose ***Suicidal ideation				

In the same 10-5-07 submission, Pfizer also provided information from the similar but earlier analysis in the PSUR. The cutoff date was not specified but there was a smaller total number of patients (N=4,906 varenicline-treated patients).

Table 3.3.1.1b: Sponsor's PSUR analysis

Treatment group	Varenicline	Placebo
Total subjects	4,906	1,487
Total patient-years	Not provided	Not provided
Number of suicidal events	4	2

This analysis included events occurring more than 7 days after treatment. The individual events are summarized in the sponsor's table below. Pfizer did not provide a reconciliation of this PSUR analysis and the update of 10-5-07, but there were four more events captured by this earlier analysis, as shown below.

Sponsor's table from PSUR excerpt, 10-5-07: Clinical study data

PID Age/Race/Gender <sup>a</sup>	Investigator term	AE/ SAE (Y/N)	Event onset/drug stop day <sup>b</sup>	Causality (investigator)	Comments
<b>Varenicline</b>					
103510121089 45/W/F	Suicidal ideation	Y/Y	74/73	Other illness (major depression)	Subject stopped varenicline treatment after deciding to resume smoking, next day experienced suicidal ideation. Had hx of recurrent major depression.
104410011012 23/W/F	Suicidal Ideation	N/Y	96/85	Study drug	Onset was 11 days after dosing completed. Concurrent life stressors were upcoming marriage and family turmoil.
103510121069 61/W/M	Suicide	N/Y	196/169	Other illness (major depression)	Subject completed 24 weeks of varenicline treatment and 27 days later committed suicide by hanging himself; hx of major depression
101650350037 43/W/F	Intentional overdose	Y/N	71/84	Study drug	Subject took 1 mg above maximum allowable dose for 2 days during treatment; completed treatment at allowable doses.
<b>Placebo</b>					
103610141106 69/W/M	Suicidal ideation	Y/N	65/83	Study drug	Limited information available, no hx of psychiatric illness.
100750240523 34/W/M	Suicide attempt (intentional drug overdose)	N/Y	35/17	Other (relational problems not otherwise specified)	Subject withdrew consent after 17 days on treatment, 18 days later attempted suicide by consuming 150 acetaminophen/ diphenhydramine and 6-12 beers; no hx of psychiatric illness, but underlying stress

Comment: As shown, suicidal events were infrequently reported in the varenicline clinical trials. One completed suicide occurred post-varenicline treatment. It should be recalled that subjects with active psychiatric illnesses were generally excluded from these clinical trials. Also, there could well have been under-ascertainment of such events since these trials were not designed with neuropsychiatric events as a specific outcome. Actual suicide attempts might have come to the



attention of the investigators more readily than suicidal ideation. Also, the sponsor's search for and adjudication of events was not conducted according to the more rigorous methods that have been developed in recent years to categorize suicidal adverse event data (as were used in the recent analysis of suicidal events with anticonvulsant drugs, for example). These methods involve an expanded search for events, including review of all serious adverse events, and blinded adjudication of the candidate cases. To the extent that these searches may be more sensitive, some cases of suicidal events may have been missed by searching only for selected preferred terms.

On balance, the clinical trial data are inconclusive; they do not show an association between varenicline treatment and suicidal adverse events, but they are not adequate to rule out such an association with any degree of confidence, and there may have been under-ascertainment of events. It is not clear that even an expanded search would necessarily disclose sufficient numbers of events for a meaningful comparison.

#### 3.3.1.2 Chantix-suicidality-related submission on postmarketing cases (U.S. and foreign).

Pfizer described their analysis of postmarketing suicide-related events in the PSUR excerpt submitted 10-5-07. They searched their global postmarketing report database for adverse events coded by one of the aforementioned MedRA suicide/self-injury SMQ preferred terms, during the period 5-10-06 to 5-9-07. Pfizer estimated worldwide exposure during this time frame as roughly 2 million patients. Their search yielded a total of 102 cases, none of which involved completed suicide. Of these 102 cases, 73 (72%) involved females; a slight majority of the cases (59/102 or 58%) were consumer reports. The most frequent MedDRA Preferred Term was suicidal ideation (81/102 or 79%). Pfizer adjudicated 19 of the 102 (19%) cases as having a "possible causal relationship" to varenicline treatment. The remaining majority of the cases were found either to lack sufficient detail, to involve a patient with a pre-existing psychiatric disorder, or to involve a concomitant antidepressant medication. Pfizer concluded from their review that there was "insufficient evidence to support an association between varenicline and the reported suicide-related events..." In the 10-5-07 submission, Pfizer included an updated count of suicide-related postmarketing events for the period 5-10-07 to 9-9-07. This search added an additional 74 cases, which were not described in detail but were deemed "consistent with the analysis provided in the prior report..."

### 3.2.2 Disproportionality analyses

#### 3.2.2.1 Pfizer's data mining analysis

Pfizer performed a data mining analysis of postmarketing reports of suicidal events for the EMEA; the results were included in their 10/5/07 submission to FDA. The data were obtained from FDA's AERS database through 2006 and from the WHO database through the first quarter of 2007. For context, note that marketing of varenicline was approved by FDA in May 2006 and by the EMEA in September 2006. The adverse events analyzed were those with MedDRA preferred terms (PT) for suicide/self injury (as employed in the analysis of clinical trial data) plus a customized event term consisting of all of these PTs. The comparators were nicotine and Zyban. Using the customary cut-off of 2 times expected for an lower bound of the confidence interval of the empirical bayesian estimate (EB05) score, the results indicated disproportionate reporting with Zyban for suicidal ideation (EB05 = 2.9), and for suicide attempt (EB05 = 2.4). The sponsor reported only a single report identified with varenicline, involving suicidal ideation.

Comment: The paucity of reports in the sponsor's data mining analysis for varenicline is likely a reflection of the time frame covered by the analysis, which was fairly early in the marketing

history of varenicline. The sponsor's analysis is of little inferential value with respect to the assessment of suicidal adverse events with varenicline treatment.

### 3.3.2.2. FDA data mining analysis

Data mining using FDA's WebVDME tool was performed for varenicline (as a suspect drug) on AERS data current through December 7, 2007.<sup>60</sup> Of the 12 suicide/self-injury preferred terms noted previously, 10 had EB05 scores 2.0. The results for the other two terms are displayed below.

Table 3.3.2.2.a AERS Data mining results for varenicline, 12-7-07:  
Suicide/self injury terms with EB05 $\geq$ 2.0

PT	N	EB05	EBGM*	EB95
Suicidal behaviour	13	2.839	4.571	7.166
Suicidal ideation	143	3.311	3.806	4.357

\* Empirical Bayesian Geometric Mean

For comparison, data mining was performed on AERS data through February 28, 2008 for trade named nicotine products<sup>61</sup> and for Zyban.

None of the 12 suicide/self-injury preferred terms were associated with an EB05  $\geq$ 2.0 for any trade name nicotine product.

The results for Zyban are displayed below.

Table 3.3.2.2.b AERS Data mining results for Zyban, 2-28-08:  
Suicide/self injury terms with EB05 $\geq$ 2.0

PT	N	EB05	EBGM*	EB95
Suicide attempt	85	2.016	2.416	2.877
Suicidal ideation	104	2.8	3.298	3.863

\* Empirical Bayesian Geometric Mean

Thus, FDA's data mining results showed disproportionate reporting for the PT suicidal ideation with both Zyban and varenicline, for suicide attempt with Zyban, and for suicidal behavior with varenicline. No PTs from the suicide/self-injury MedDRA SMQ were associated with an EB05 greater than or equal to 2.0 for nicotine products.

### 3.2.3 Expert report for Pfizer

Pfizer submitted a report by Dr. John R. Hughes, professor in the departments of Psychiatry, Psychology and Family Practice at the University of Vermont., on smoking cessation and suicide. Dr. Hughes reviewed the literature and came to several conclusions, which will be summarized briefly here. The discussion of the literature itself will be found in the section that follows.

Dr. Hughes reviewed approximately 120 publications identified from a PubMed search for articles dealing with the topics of suicide, smoking, nicotine, etc. His report also discusses some theoretical mechanisms for a relationship between smoking and suicidal behaviors. His

<sup>60</sup> All data mining results were provided by Dr. Joseph Tanning, OSE

<sup>61</sup> Nicotine trade name products: Commit, Habitrol, Nicoderm, Nicopatch, Nicorette, Nicotine Dermal, Nicotine Gum, Nicotine Polacrilex, Nicotine Resin, Nicotine Transdermal, Nicotinell, Nicotrol, Niquitin, Niquitin Cq, Prostap

conclusions that are relevant to the current analysis of suicidal events with varenicline are as follows.

- a) First, smoking has been shown to be associated with suicide in many studies of various designs, and this association applies to completed suicide as well as suicidal ideation.
- b) Secondly, smoking cessation is associated with worsening mood but has not been linked specifically to suicide, although there are reports of suicidal ideation occurring post-cessation.
- c) Thirdly, nicotinic medications have not been associated with suicide.

### **3.3.4 Literature review for varenicline and psychiatric events**

Pfizer submitted (10-5-07) a literature review on the topics of smoking cessation, suicide, and varenicline, and their report included a total of 53 references. The Expert Report by J.R. Hughes from the same submission presented a total of 67 literature references, although there was some overlap between the list submitted by the expert and that submitted by the sponsor. Highlights of the sponsor's literature review are summarized below, supplemented by some additional references identified by this reviewer.

#### **3.2.3.1 Smoking is associated with suicidal behavior**

The sponsor provided numerous citations of studies with various designs (surveys, prospective cohort, case-control for completed suicide) showing an association between suicidal ideation, suicide attempts, and completed suicide with smoking. In fact, some studies have shown a dose-relationship; a prospective study of military personnel showed a higher risk for completed suicide among those who smoked more than one pack per day.<sup>62</sup> A recently published four-year prospective study of German youth, too recent to be included in the sponsor's list of references, once again found an association between smoking and subsequent suicide attempts; however, previous suicidal ideation or attempt was not associated with subsequent smoking.<sup>63</sup>

#### **3.2.3.2 Smoking cessation is associated with depressed mood**

Depressed mood is listed as one of the symptoms of nicotine withdrawal in the American Psychiatric Association's Diagnostic and Statistical Manual-IV; some other symptoms include poor concentration, hunger, anxiety, insomnia, restlessness, and irritability.<sup>64</sup> Depressed mood can appear as a symptom within 24 hours of smoking cessation.<sup>65</sup> With respect to frank major depressive disorder as a complication of smoking cessation, Hughes (Pfizer's consultant) recently published a review of seven studies and concluded that definitive data are lacking on whether smoking cessation puts patients at higher risk of major depressive disorder.<sup>66</sup>

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<sup>62</sup> Miller M, Hemenway, D., Bell, NS., et al. Cigarette Smoking and Suicide: A Prospective Study of 300,000 Male Active-duty Army Soldiers. *Am J Epidemiol.* 2000;151:1060-1063.

<sup>63</sup> Bronisch, T., H6fler, M., Lieb, R. Smoking predicts suicidality: Findings from a prospective community study. *J Affect Disord* 2008;108:135-45.

<sup>64</sup> American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. American Psychiatric Association, Washington, DC, 1994.

<sup>65</sup> West R, Ussher M, Evans M, Rashid M. Assessing DSM-IV nicotine withdrawal symptoms: a comparison and evaluation of five different scales. *Psychopharmacology* 2006; 184:619-627.

<sup>66</sup> Hughes JR. Depression during tobacco abstinence. *Nicotine Tob Res.* 2007 (4):443-6.

### 3.2.3.3 There is an absence of data showing that smoking cessation is a risk factor for suicide

Although it is reasonable to assume that a condition associated with depressed mood might also be associated with suicidal behaviors, neither the sponsor nor this reviewer could locate literature clearly supporting smoking cessation or nicotine withdrawal as risk factors for suicide per se. In fact, a meta-analysis of three long-term smoking cessation intervention randomized controlled trials that recorded suicide as an outcome showed a numerically smaller risk of completed suicides among the smoking cessation intervention subjects (10/8740) than among the usual care comparison subjects (15/6786), although the difference was not statistically significant.<sup>67</sup> However, given the challenges inherent in studying suicidal behaviors, the absence of such data should not be interpreted as evidence against such an association.

### 3.2.3.4 Smoking is associated with major psychiatric disorders

A recent publication of data from the National Epidemiologic Survey on Alcohol and Related Conditions, which involved over 43,000 respondents, showed that smoking is associated with a variety of major psychiatric disorders,<sup>68</sup> but the association was not as strong for smokeless tobacco.<sup>69</sup> Indeed, the survey estimates that close to half of all U.S. cigarette consumption is by individuals with psychiatric disorders.<sup>70</sup>

## 3.2.4 Case reports in the literature of psychiatric disorders associated with varenicline

There have been two published reports of schizophrenia (42-year-old female),<sup>71</sup> and mania (63-year-old male),<sup>72</sup> experienced while the patients were taking varenicline for a few days and for one week respectively. In both of these cases, varenicline appeared to exacerbate the patient's pre-existing psychiatric disease (schizophrenia and bipolar disorder respectively). Varenicline likely contributed to these events due to the temporal onset and positive dechallenges.

In a third published report, a 41-year-old female, with history of bipolar II disorder and polysubstance abuse,<sup>73</sup> discontinued varenicline after 3 days because she felt irritable, 'wacko' and that her 'skin crawled.'<sup>74</sup> These events resolved. The patient then started another regimen of varenicline for several weeks and was then hospitalized due to *suicidal ideation* as well as

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<sup>67</sup> Leistikow BN, Shipley MJ. Might stopping smoking reduce injury death risks? A meta-analysis of randomized, controlled trials. *Prev Med.* 1999; 28: 255-9.

<sup>68</sup> Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry.* 2004 61(11):1107-15.

<sup>69</sup> Goodwin RD, Zvolensky MJ, Keyes KM. Nicotine dependence and mental disorders among adults in the USA: evaluating the role of the mode of administration. *Psychol Med.* 2008 Mar 26;:1-10 (epub).

<sup>70</sup> Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry.* 2004 61(11):1107-15.

<sup>71</sup> Freedman R. Exacerbation of schizophrenia by varenicline (letter). *Am J Psychiatry* 2007;164:1269.

<sup>72</sup> Kohen I, Kremen N. Varenicline-induced manic episode in a patient with bipolar disorder. *Am J Psychiatry* 2007;164:1269-70.

<sup>73</sup> Abstinent from alcohol and amphetamines for 3 months and 3 years respectively.

<sup>74</sup> Morstad AE, Kutscher EC, Kennedy WK, Carnahan RM. Hypomania with agitation associated with varenicline use in Bipolar II Disorder. *Annals of Pharmacotherapy*: epub 15 Jan 2008.

hopeless feelings, agitation and racing thoughts. The patient had a positive dechallenge. The patient experienced a similar episode 10 years earlier. The patient was taking bupropion, oxcarbazine, quetiapine for  $\geq 1$  year and clonazepam for 5 months. Although the patient's psychiatric history was a contributing factor, varenicline could have exacerbated her condition.

### 3.2.5 Reporting Rates for suicidal events

The table below displays the reporting rates for any suicidal event (suicidal ideation or suicide attempt) and for overt self-injury events, for each drug product, during the first two calendar years in which the drug was on the market.

Table 3.3.6.1 Reporting rates for suicidal events, first two calendar years of marketing

Drug Product	Years	Total RXs*	All suicidal reports received	Self-harm reports received	All suicidal reports / 100,000 Rx	Self-harm reports/ 100,000 Rx
Nicotine patch	1991-2	8,877,975	1	1	0.01	0.01
Zyban	1997-8	3,130,255	11	3	0.35	0.10
Chantix	2006-7	8,164,315	153	36	1.90	0.44

\*Source: Verispan, LLC: Vector One®: National (VONA). See Table 2 in Appendix 4.

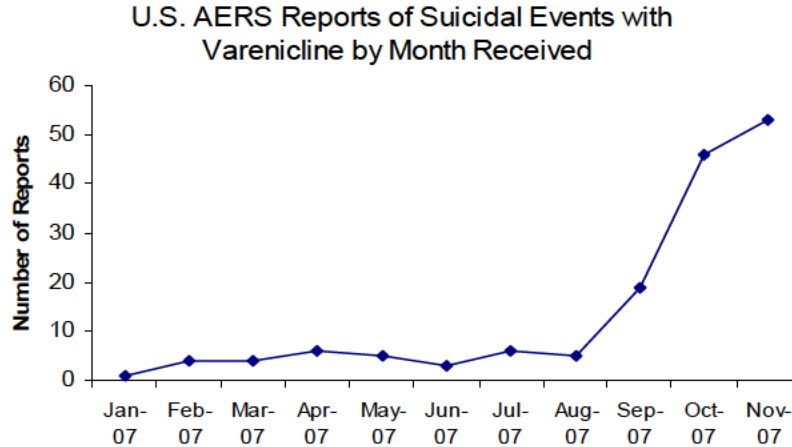
It can be seen that varenicline had the largest number of such reports, both in terms of absolute numbers and in proportion to prescriptions, during the first two calendar years in which the products were marketed. This is made clear by the reporting rate ratios, displayed below.

Table 3.3.6.2 Reporting rate ratio, first 2 calendar years of marketing

	All suicidal event reports	Self-harm reports
Chantix nicotine patch	166.4	39.1
Chantix:Zyban	5.3	4.6

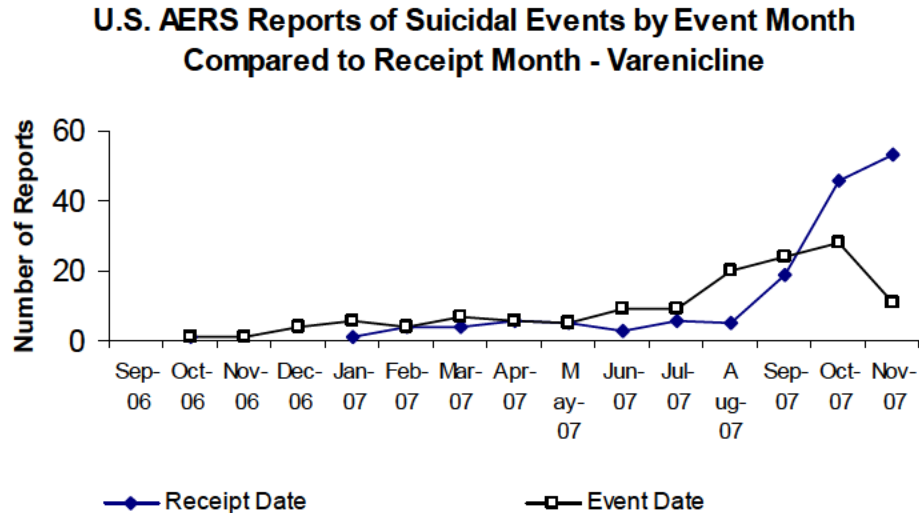
The following graph (Figure 1) displays the numbers of U.S. suicidal events reported for varenicline according to the month the report was received. By November the monthly number of reports was roughly 10-fold higher than it had been earlier during 2007. (For comparison, a similar graph for Zyban is included in the appendix.)

Figure 1



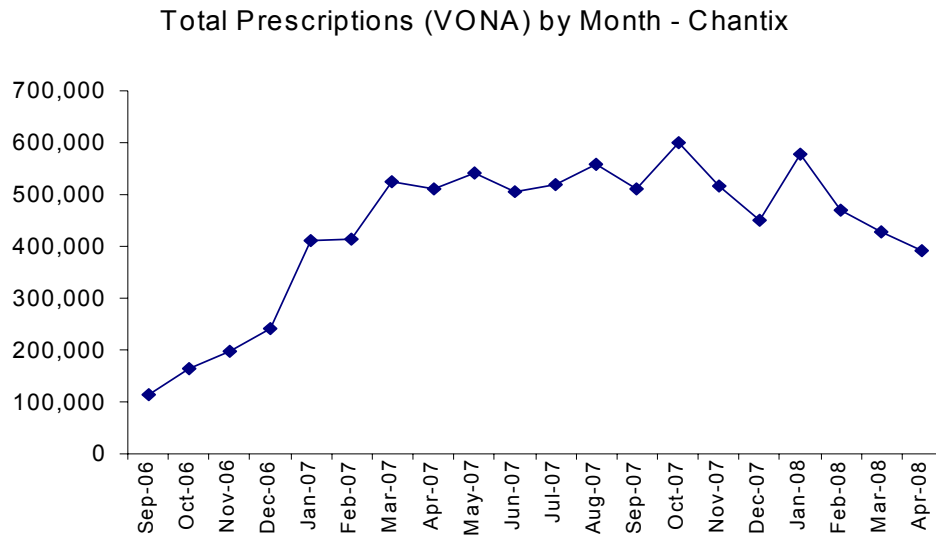
The following graph (Figure 2) displays the monthly numbers of reports according to the date received and the date of the event. The discrepancy between the two reflects the cases that were reported retrospectively.

Figure 2.



In contrast to the number of reports received, prescribing of varenicline did not increase at the end of 2007, as shown in the following graph (Figure 3).

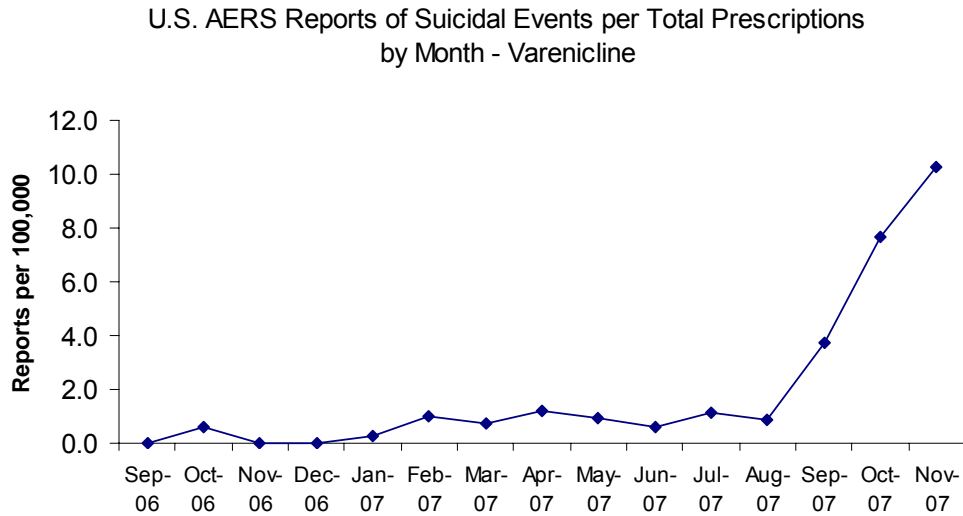
Figure 3.



*Source: Verispan, LLC: Vector One®: National (VONA) September 2006 through April 2008*

The next graph (Figure 4) displays the reporting rate by month; i.e., the number of suicidal events reported divided by the prescriptions dispensed for each month. If the higher number of reports in the final months of 2007 was accounted for by a corresponding increase in prescriptions, we would expect this graph to be close to a flat line.

Figure 4.



*Source: Verispan, LLC: Vector One®: National (VONA), September 2006 through November 2007*

### 3.2.6 Status of OSE's efforts to obtain observational Chantix psych-related safety data from observational sources.

We attempted to ascertain whether an observational study of the association of varenicline treatment with psychiatric events would be feasible using the epidemiology resources available to FDA (namely, the existing epidemiology research contracts). OSE queried the four epidemiology sites currently under contract regarding the number of users of varenicline or comparator products in their respective databases, to determine if an observational study using any or all of these sites would be fruitful. The results are shown below. Also indicated is the number of varenicline users in the VA MedSAFE database; this is not formally one of FDA's research contract databases, but the FDA has collaborated with this group in the past.

Table. 3.3.7.1 Use of smoking cessation aids in the epidemiology contract research databases and VAMedSAFE.

*[\*\*Note: These are proprietary data obtained by FDA and cannot be released to the public/non-FDA personnel without approval obtained through the FDA/CDER Office of Surveillance and Epidemiology. \*\*]*

<b>Varenicline</b>	Total Users	Time Period
Kaiser Permanente North and South	4,654	Thru Oct 2007
HMO Research Network	20,917	varies by site
i3	6,260	Thru Jun 2007
Tenn Care (Vanderbilt)	1,941	Thru Mar 2007
<i>VAMedSAFE</i>	<i>27,491</i>	<i>Thru Sep 2007</i>

<b>Zyban (bupropion)</b>	Total Users	Time Period
Kaiser Permanente North and South	n/a	-
HMO Research Network	7,280	varies by site
i3 Ingenix	7,833	Thru Jun 2007
Tenn Care (Vanderbilt)	652,778	2003-Mar 2007

In preliminary assessment of the VA database, among the 27,491 varenicline users in the VA database, there were 48 patients with an inpatient diagnosis of a psychotic disorder following a prescription for varenicline, including 14 with no diagnosis of a psychotic disorder inpatient or outpatient during the preceding year.

On 3-18-08 the DVA indicated they were beginning a comparative analysis of the rate of hospitalization for psychosis among roughly 27,000 varenicline users, 100,000 nicotine replacement users, and 12,000 bupropion users. The preliminary data suggested a slightly higher rate among varenicline users. They also have developed a protocol outline for this study.

An additional avenue for study may be the Department of Defense data system; at initial contact their health care claims database was current only through 2005. The database is expected to be updated in the spring. Therefore, no information was available at the time of writing. USAGE

## 3.3 DRUG USAGE PATTERNS

### 3.3.1 Wholesale Volume

Wholesale distribution patterns for the smoking deterrents class USC 69000 revealed that in year 2007, the volume of these products sold (in tablets, individual patches, gums, etc.) nearly doubled from the previous year from 369 million to approximately 684 million extended units, respectively (Appendix 5: Table 1). Varenicline was the most widely distributed product from



manufacturers to U.S. wholesalers, accounting for over 60% of the market, followed by nicotine products (gums, transdermal patches, etc.) with nearly 32%. Bupropion products accounted for less than 2% of the market in year 2007. During the previous year, nicotine products (of which transdermal patches accounted for nearly 20% of sales) accounted for nearly 71% of the market, and bupropion products (Zyban<sup>®</sup>, Buproban<sup>®</sup>) accounted for approximately 6% of the market.

### 3.3.2 Dispensed Prescriptions

#### 3.3.2.1 Smoking deterrents market, USC 69000

Dispensed prescriptions for the “smoking deterrents” market, USC 69000, has undergone a dramatic shift in usage patterns during years 1991 through 2007 (Appendix 5: Figure 1, Table 2). Between years 1991 through 1996, nicotine transdermal and nicotine chewing gum products dominated the dispensed prescription market for “smoking deterrents.” Dispensed prescriptions for nicotine transdermal patches approached 9 million during year 1992 then dropped to half that amount during year 1993 to 4 million prescriptions then dropped again to less than half a million prescriptions a year from year 1997 onward. From year 1997 to 2004, bupropion products overtook the “smoking deterrents” market and rose sharply to nearly 2.5 million dispensed prescriptions in year 1998 then declined steadily year after year to less than 60,000 dispensed prescriptions in year 2007. Dispensed prescriptions for the “smoking deterrents” market rose sharply again during year 2006 and 2007 with the introduction of varenicline. During year 2007, varenicline accounted for nearly 94% of the “smoking deterrents” market followed by nicotine transdermal patch products at 3.5% of the market. Bupropion products accounted for less than 1% of the market.

#### 3.3.2.2 New, Continuing, Switch/Add-On and Prior Rx Prescriptions

For the prescription only products, varenicline and bupropion, we examined dispensed prescription activity to determine which of those new prescriptions were being dispensed as new-patient prescriptions, continuing-patient prescriptions and switch/add-on prescriptions. During year 2007, approximately 63% of new prescriptions for varenicline were dispensed as new-patient prescriptions indicating that no prior prescriptions were dispensed for this product in the previous six months (Appendix 5: Figure 2).<sup>75</sup> Approximately 37% of varenicline prescriptions were dispensed as continuing-patient prescriptions, indicating that these patients were on prior therapy with varenicline in the previous six months. Less than 1% of varenicline prescriptions were dispensed as a switch or add-on therapy to those who were on *any* smoking deterrent therapy in the previous six months.

Of those who were either adding or on prior therapy with a smoking deterrent product in the previous six months, nearly 14% of dispensed prescriptions for varenicline were preceded by a bupropion product. The majority of prior therapies were some type of nicotine replacement product (Appendix 5: Table 3).<sup>76</sup>

For bupropion products, approximately 67% of new prescriptions for bupropion products were dispensed as new-patient prescriptions and 25% were dispensed as continuing-patient prescriptions during year 2007. Approximately 7.5% of bupropion prescriptions were dispensed

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<sup>75</sup> Verispan, LLC. Vector One®: National. Extracted March 2008. File: VONA 2007-2425 3-6-08 Chantix RxType.qry

<sup>76</sup> Verispan, LLC. Vector One®: National. Extracted March 2008. File: VONA 2007-2425 3-6-08 Chantix PriorRx.qry

to those who were either adding or on prior therapy with *any* smoking deterrent product in the previous six months (Appendix 5: Figure 3).<sup>77</sup>

Of those who were either adding or on prior therapy with a smoking deterrent product in the previous six months, approximately 81% of dispensed prescriptions for bupropion were preceded by varenicline (Appendix 5: Table 4).<sup>78</sup> This indicates a low rate of persistency for varenicline.

### 3.3.3 Patient Demographics

Patient characteristics for those patients filling a prescription for varenicline in the outpatient retail pharmacy setting revealed that approximately 4.3 million unique patients have received a prescription for varenicline over years 2006 and 2007. The majority of use fell among the age 50-59 year group (29%), followed by the age 40-49 year group (28%) (Appendix 5: Table 5, Figure 4)<sup>79</sup>. Less than 1% of use was among patients less than 20 years of age. Use was more prevalent among female patients for all age groups except for the age 0-9 year group which had a slightly greater use in males versus females.

Patients receiving a dispensed prescription for bupropion products for smoking cessation, Zyban® and Buproban® had similar usage patterns in terms of age and gender (Appendix 5: Table 6, Figure 5)<sup>80</sup>. For the combined years 2002 through 2007, the majority of use was among the age 40-49 years (30%) followed by age 50-59 years (24%). More females used bupropion products than males for all age groups except ages 50-59 years and 0-9 years.

Utilization data by patient age and gender was not available for OTC nicotine replacement products.

### 3.3.4 Concurrency Analysis with Antidepressants-Antipsychotics-Anxiolytics

Examination of concurrent use revealed that in year 2007, approximately 39% of patients on varenicline were on concurrent therapy with a product in the antidepressant-antipsychotic-anxiolytic market (Appendix 5: Table 7). The most common class of products used concurrently with varenicline were SSRI's (19%) followed by benzodiazepines (16%). Likewise, patients on Zyban® or Buproban® showed similar concurrency rate. The most common class of products used concurrently with Zyban® or Buproban® were New Generation Antidepressants (17%), SSRI's (16%), followed by benzodiazepines (14%) (Appendix 5, Table 8).

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<sup>77</sup> Verispan, LLC. Vector One®: National. Extracted March 2008. File: VONA 2007-2425 3-6-08 zyban RxType.xls

<sup>78</sup> Verispan, LLC. Vector One®: National. Extracted March 2008. File: VONA 2007-2425 3-6-08 zyban PriorRx.xls

<sup>79</sup> Verispan, Vector One®: Total Patient Tracker. Years 2006 - 2007. Extracted March 2008. File: TPT 2007-2425 Chantix AgeGender Aggregate May06-Dec07 3-6-08.xls, TPT 2007-2425 Chantix AgeGender May06-Dec07 3-6-08.xls

<sup>80</sup> Verispan, Vector One®: Total Patient Tracker. Years 2002 - 2007. Extracted March 2008. File: TPT 2007-2425 Bupropion Age Gender Y02-07 3-8-08.xls, TPT 2007-2425 Bupropion AgeGender Aggregate 02-07 3-8-08.xls

## 4 DISCUSSION

### 4.1 AERS CASES

In this review, three smoking cessation products (varenicline, bupropion, and transdermal nicotine) were evaluated for a possible association of their use to suicide related events. For all three drugs, the AERS database revealed 262 reports with suicidal events that were mostly suicidal ideation (68%) and the remainder involved suicide (attempt or completed) or other self-injury (32%). The majority of the 262 reports involved varenicline (n=153; 58%) followed by bupropion (n=75; 29%) and nicotine transdermal patch<sup>81</sup> (n=34; 13%). Varenicline cases had a higher proportion of ideation cases (116/153; 76%) compared to bupropion (46/75; 61%) and nicotine (n=16/34; 47%). Varenicline case series had the lowest proportion of suicide (attempt or completed) cases (37/153; 24%) compared to bupropion (29/75; 39%) and nicotine (18/34; 53%). More than half (8/13) of the nicotine suicide cases originated from a single literature report.<sup>82</sup>

Most of the varenicline cases (91%) co-reported other psychiatric-related events in addition to the suicidality. This trend was lower with bupropion (only one-half of the cases had such co-reported events) and nicotine (about a quarter had such co-reported events). Where there were co-reported psychiatric-related events, depression was the most common for all 3 drugs (varenicline 69/139 [50%]; bupropion 26/34 [76%] and nicotine 5/8 [62%]). This is not surprising as suicide can be preceded by depression.<sup>83,84</sup>

Among the 262 AERS reports, there were more females (61%) than males (36%).<sup>85</sup> This ratio of 2 to 1 female to male patients was seen with varenicline (69% to 32%) and nicotine (61% to 39%); there was a smaller difference in gender with bupropion (53% to 47%). Pfizer's suicidality analysis of varenicline postmarketing reports also identified more female (79%) than male patients (21%).<sup>86</sup> Drug usage data (see Appendix 4) showed similar gender trends (female vs. male) as the AERS data for patients that were taking varenicline (66% to 45%) and bupropion (51% to 49%). Drug usage data for patient gender (or age) for nicotine was not available.

For all 3 drugs, the median patient age was similar (varenicline 45 years, bupropion 41 years and nicotine 41.5 years). Pfizer's postmarketing suicidality analysis for varenicline postmarketing reports also identified a median age of 49.3 years. The ages of the AERS cases were also comparable with the drug use data; for varenicline, the two largest patient age groups were between 40 and 59 years and for bupropion, the largest group was between 40-49 years. Among the 262 AERS reports, there were 3 pediatric cases (all suicides and 15-years-old; bupropion, n=2; nicotine, n=1).

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<sup>81</sup>Nicotine transdermal patch will hereafter be referred to as 'nicotine.'

<sup>82</sup>Woolf A, Burkhart K, Caraccio T, Litovitz T. Self-poisoning among adults using multiple transdermal nicotine patches. *J. Toxicol. Clin Toxicol.* 1996;34:691-698. Nine adults intentionally overdosed on multiple transdermal nicotine patches. This was from a prospective post-marketing surveillance project from U.S. poison centers

<sup>83</sup>Oquendo MA, Galfalvy H, Russo S, Ellis SP et al. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. *Am. J. Psych.* 2004;161:1433-1441.

<sup>84</sup>An AERS review of other non-suicidal psychiatric events (including *depression*) with smoking cessation drugs will be the subject of a future OSE consult.

<sup>85</sup>In 4% of the cases, gender was unknown.

<sup>86</sup>Mentioned in **3.3. Epidemiology**; There were initially 102 reports (received by Pfizer between 5/10/06 and 5/9/07) with suicidal events. After exclusions, 92 reports were evaluated gender was female (n=67), male (n=18) and unknown (7). The 92 Pfizer reports are not necessarily all included in the DAEA II AERS case series (n=153).

In almost all cases (95 to 98%) for the 3 smoking cessation drugs, the recommended dose was used (when known) implying that under or overdosing was an unlikely explanation for the reported events. The median time to event onset was less than two weeks for all three drugs. In most of the cases for varenicline (72%) and bupropion (89%) and in half for nicotine (50%), the suicide related events occurred while the patients were on smoking cessation therapy compared to the event occurrence *after discontinuation* (varenicline 12%, bupropion 7%, nicotine 6%). Although FDA's Varenicline Healthcare Advisory<sup>87</sup> mentioned that some patients experienced neuropsychiatric events after varenicline withdrawal, the varenicline labeling does not contain this information.

For all three drugs (n=262), almost one-half (45%) of the patients had a psychiatric history; one quarter (25%) of the cases reported no psychiatric history and for about one-third (31%) it was unknown. Bupropion (24/75; 32%) had the most cases with no reported psychiatric history, followed by varenicline (40/153; 26%) and nicotine (1/34; 3%). Nicotine had the most (22/34; 65%) cases *with* reported psychiatric history followed by varenicline (77/153; 50%) and bupropion (18/75; 24%).

For all three drugs (n=262), approximately one-quarter (23%) of the patients did not report the concomitant use of any psychiatric-related medications and/or other medications that were labeled for suicidal events;<sup>88</sup> approximately one-third (34%) of the cases reported concomitant use of other psychiatric medications and in the remainder (43%), this information was unknown. Bupropion had the most cases with no concomitant psychiatric medications (25/75; 33%) followed by varenicline (32/153; 21%) and nicotine (3/34; 9%). Varenicline (60/153; 39%) and nicotine (15/34; 44%) had more cases citing the use of concomitant psychiatric medications than bupropion (14/75; 19%). The most common concomitant psychiatric medication reported was antidepressants for all three drugs: varenicline (48/153; 31%), bupropion (7/75; 9%) and nicotine (12/34; 35%).

For all drugs (n=262) there were 84 (32%) cases where it was explicitly reported that the patient's suicidal event was a significant behavior change from the past (new experience or pre-existing disease worsening; Appendix 1-3). In more than half of the 84 cases (n=48; 57%) the patient never had such an experience until the exposure of the smoking cessation drug and in the remaining cases (n=36; 43%) there was a worsening of pre-existing disease. Varenicline had the most cases of significant behavior changes (63/153; 42%) compared to bupropion (11/75; 15%) and nicotine (4/34; 12%) which were about the same. Varenicline had the most cases of these suicidal-related-behavior changes being a first-time experience (37/153; 24%), followed by bupropion (11/75; 15%); nicotine had none. Varenicline also had more cases of disease worsening (26/153; 17%) compared to nicotine (4/34; 12%) and bupropion (6/75; 8%). Depression was the most common pre-existing psychiatric condition that was reported to have worsened after drug exposure with varenicline (14/26), bupropion (3/6) and nicotine (4/4).

A similar proportion of cases for varenicline (35%) and bupropion (33%) reported a positive dechallenge; nicotine cases reported fewer cases (24%). In these positive dechallenge cases, the patients developed suicidal thoughts or behavior after starting the smoking cessation drug and

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<sup>87</sup>FDA Public Health Advisory: Important Information on Chantix (varenicline) 2/1/08; <http://www.fda.gov/cder/drug/infopage/varenicline/default.htm>

<sup>88</sup>Of the 88 patients (for all three smoking cessation drugs) who were taking other medications, in most (n=85) cases, such medications were psychiatric related some of which [e.g., antidepressants] were labeled for suicide. There were only a few patients (n=3) that were taking other *non*-psychiatric-related medications that were labeled for suicide. Therefore 'concomitant psychiatric medication' will be used hereafter to describe the entire group of these other medications.

these suicidal events resolved after the drug was discontinued. Three cases (varenicline, n=1; bupropion, n=2) reported a positive *rechallenge* where the patient again experienced a suicidal event after re-introduction of the smoking cessation product.

Most (varenicline, 96%; bupropion 79%) or all (nicotine) of the cases had a serious outcome. For the outcome of hospitalization, nicotine had the most reports (38%), followed by bupropion (28%) and varenicline (12%). In almost three-quarters (13/18) of the nicotine cases of suicide (completed or attempt), due to lack of information in the reports, it was not able to be determined if the patient was using the patch for a smoking cessation indication. This made it difficult to assess any association with the *therapeutic* use of the patch with completed or attempted suicides.

The proportion of fatal cases (completed suicides) was similar for all three drugs (varenicline [18/153; 12%], bupropion [10/75; 13%] and nicotine [5/34; 15%]). Of the fatalities, there were few with no contributing factors<sup>89</sup> reported (varenicline [1/18; 6%], bupropion [1/10; 10%] and nicotine none). Completed suicides with varenicline had more contributing factors (28%) than nicotine (20%) or bupropion (10%). However, information on such contributing factors was unknown more often with bupropion and nicotine (both 80%) compared to varenicline (67%).

Six of the 10 fatal bupropion cases reported the method of suicide, including the use of a gun (n=4), hanging (n=1), and drug overdose (n=1). In the remaining four cases, the method of suicide was unknown. Five of the 18 fatal varenicline cases reported the use of a gun (n=3) or drug overdose (n=2). In the remaining 13 cases, the method of suicide was unknown. Five completed suicides were reported with nicotine (drug overdose, n=3, unknown method, n=2); no weapons were involved in any of them.

## **4.2 REVIEW OF CLINICAL TRIALS, SPONSOR SUBMISSIONS, AND THE LITERATURE**

Clinical trial data for varenicline is not adequate to either rule in or rule out an association between suicidal behaviors and varenicline treatment, owing to the small number of such events reported in the trials. It is not clear if an expanded search for suicidal events in the clinical trial database would yield a sufficient number of events for a meaningful analysis. It should be borne in mind that patients with active psychiatric disorders were by and large excluded from the clinical studies.

Disproportionality analyses (data mining) of AERS report data for smoking cessation products shows disproportionate reporting of suicidal ideation and behaviors for varenicline and Zyban, but not nicotine.

Evidence in the literature supports (1) an association between smoking and suicidal behaviors, including completed suicide; (2) an association between psychiatric disorders and smoking; and (3) an association between nicotine withdrawal and depressed mood. There is a lack of published data to indicate that smoking cessation is a risk factor for suicidal behavior.

Observational data on the occurrence of psychiatric disorders with varenicline treatment may soon be available from the Department of Veterans Affairs, and possibly from the Department of Defense.

Varenicline showed a higher reporting rate for any type of suicidal event and for self-harm in comparison to Zyban, and even higher rates in comparison to transdermal nicotine, during the first two calendar years in which each product was marketed. There are several limitations to this

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<sup>89</sup>Contributing factors are history of psychiatric disease and or medications indicated for psychiatric disease and non-psychiatric medications labeled for suicidality as an adverse events.

analysis, however. First, we used receipt date as stated in the AERS database, instead of the date of the event (which requires a hands-on review of the text of the report for validation). Obviously, stimulated reporting attending publicity regarding Chantix may have played a role in the higher frequency of reporting for varenicline.

There may have been changes in reporting practices during the time span since transdermal nicotine was marketed (which predated the MedWatch program). Also, since data on indication is lacking, we were unable to precisely quantify how much bupropion was used for smoking cessation, and were limited to using prescriptions specifically for the brand Zyban product as a proxy. Nonetheless, there is a clear discrepancy in the levels of reporting of these events for the three products examined. Stimulated reporting, on the basis of the publicity surrounding adverse effects of varenicline, seems a likely explanation for the substantially increased reporting rate for suicidal events observed in the latter half of 2007.

### **4.3 DRUG USAGE PATTERNS**

Findings from the drug utilization review should be interpreted in the context of the known limitations of the databases used. We estimated that these smoking cessation products are distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these non-federal hospital channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. Furthermore, IMS estimates that approximately 50% of all U.S. OTC sales activity is captured in this database<sup>90</sup>.

The dispensed prescription data provided by Verispan's Vector One®: National database captures retail prescription activity with a reasonable amount of certainty based on the large sample size of pharmacies and data projection methodology. However, data on OTC nicotine product use is not captured in this database. A reliable estimate of OTC product usage is not possible given the limitations of the drug usage databases available at the Agency's disposal. Unlike prescription transactions which capture detailed information on the drug product being dispensed as well as patient demographic data and prescribing specialty data, transactions for OTC products are not captured in the same method. Furthermore, the ease of accessibility for OTC products compared to prescription products and the PRN (as needed) nature of use make estimating OTC product usage difficult. For these reasons, the true extent of use for OTC nicotine replacement products alone or in combination with other drug products is at best underestimated in this analysis.

## **5 CONCLUSION**

### **5.1 AERS CASES**

- As of 11/27/07, the AERS database contained 153 cases of suicide related events for varenicline, 75 cases for bupropion, and 34 cases for transdermal nicotine products. Varenicline had a higher proportion of cases for suicidal ideation (76%) vs. bupropion (61%) or nicotine (47%) and a lower proportion of suicide (attempt and completed) or other self injurious behavior (24%) than the other drugs (bupropion 39%; nicotine 53%).

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<sup>90</sup> IMS Health, IMS National Sales Perspectives™ Retail and Non-Retail Sample Coverage of the Universe (09/15/06).

- Varenicline had the largest proportion of reports (24%) in which it was explicitly stated that the suicidal event(s) were a first-time significant behavior change from the past, followed by bupropion (15%) and nicotine (none). Varenicline cases had the most reports that described pre-existing disease worsening (17%) compared to nicotine (12%) and bupropion (8%); depression was the most common pre-existing psychiatric condition that worsened for all 3 drugs.
- In most of the cases for varenicline (72%) and bupropion (89%) and in half for nicotine (50%), the suicide related events occurred while the patients were on smoking cessation therapy compared to the event occurrence *after discontinuation* (varenicline 12%, bupropion 7%, nicotine 6% ).
- The AERS data suggest a possible association between suicidal events and the use of varenicline and bupropion, given that there were postmarketing cases of positive dechallenge/rechallenge, close temporal relationship between the event and drug use, and the occurrence of suicidal events in patients without any psychiatric history.
- Although suicide ideation cases for transdermal nicotine suggest a possible drug to event association, a further review of all nicotine formulations may be warranted.

## 5.2 REVIEW OF CLINICAL TRIALS, SPONSOR SUBMISSIONS, AND THE LITERATURE

- Clinical trial data for varenicline is not adequate to either rule in or rule out an association between suicidal behaviors and varenicline treatment, owing to the small number of such events reported in the trials.
- Reporting of suicidal events proportional to prescriptions dispensed during the first two calendar years of marketing has been higher for varenicline than for Zyban, and considerably higher for varenicline than for transdermal nicotine. Given that there was a substantial increase in the number of such reports for varenicline during the final months of 2007 that was not accompanied by an increase in prescriptions, it seems likely that stimulated reporting accounts for this recent increase in the number of reports of suicidal events. Accordingly, comparisons to reporting rates for other products must be interpreted with caution.
- Data mining using FDA's WebVDME application on AERS data for 12 suicidal or self-injury preferred terms returned a lower bound confidence interval estimate (EB05) equal to or greater than 2.0 times the expected for two preferred terms: suicidal behavior (EB05 = 2.8) and suicidal ideation (EB05 = 3.3). Similarly, for Zyban, suicide attempt (EB05 = 2.0), and suicidal ideation (EB05 = 2.8) had EB05 scores  $\geq 2.0$ ; however, none of the 12 suicide/self-injury preferred terms were associated with an EB05  $\geq 2.0$  for any trade name nicotine product
- An observational study of the occurrence of psychiatric events with varenicline treatment may provide useful data, and efforts are underway to conduct such a study through the Department of Veterans Affairs. Reporting of suicidal events proportional to prescriptions dispensed during the first two calendar years of marketing has been higher for varenicline than for Zyban and considerably higher for varenicline than for transdermal nicotine.

### 5.3 DRUG USAGE PATTERNS

- Wholesale distribution patterns and dispensed prescriptions for the smoking deterrents class USC 69000 revealed that during year 2007 varenicline was the most widely distributed product accounting for over 60% in sales volume and nearly 94% in dispensed prescriptions, followed distantly by nicotine products (gums, transdermal patches, etc.) with nearly 32% in sales and 3.5% in dispensed prescriptions. Bupropion products accounted for less than 2% of sales and less than 1% of dispensed prescriptions in year 2007.
- During year 2007, only a third of varenicline prescriptions were categorized as continuing therapy, whereas only a quarter were categorized as continuing therapy for bupropion products. Although we could not accurately measure the use of OTC nicotine transdermal products, there appears to be a high degree of switching within the class of smoking cessation products.
- Concurrency analysis revealed that nearly 40% of patients taking varenicline were on concurrent therapy with a product in the antidepressant-antipsychotic-anxiolytic market during year 2007. Similar results were found for patients taking Zyban<sup>®</sup> or Buproban<sup>®</sup>.
- The seriousness of the suicidality-related AERS reports for varenicline, its higher reporting rate compared to bupropion, and its foreseeable widespread future use in patients who want to quit smoking necessitate the regulatory actions mentioned below. These actions can help provide for increased awareness so that practitioners can better manage suicidal-related events in patients taking varenicline or bupropion.

## 6 RECOMMENDATIONS

### Varenicline

- a) The existing Neuropsychiatric WARNINGS, in the labeling, should be elevated to a **Box Warning**.<sup>91</sup>
- b) The current wording in the labeling ‘suicidal ideation and suicidal behavior,’ should be revised to ‘suicidal ideation and suicidal behavior *including suicide attempt and completed suicide*.’
- c) The labeling should include that “*in most cases, neuropsychiatric symptoms developed during Chantix treatment, but in others, symptoms developed following withdrawal of Chantix therapy.*”<sup>92</sup>
- d) We recommend a clinical trial to assess the safety of varenicline use and to determine the incidence of neuropsychiatric symptoms with varenicline, especially in patients with pre-existing psychiatric disorders. Ideally, such a trial would include a comparison to other smoking cessation therapies. There will of course be many design issues to consider,

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<sup>91</sup>Criteria for a Black Box Warning: Special problems, particularly those that may lead to *death or serious injury*, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. 21 CFR part 201.57(e) Warnings. April 1, 2002.

<sup>92</sup>As per Healthcare Advisory, February, 2008.



including sample size, subject selection, protections for the subjects, and comparison groups; however, a complete discussion would be beyond the scope of the present review.

### **Bupropion**

For Zyban labeling,<sup>93</sup> we recommend the following wording for the existing Box warning:

*Depression, including suicidal ideation, completed suicide and suicide attempt have been reported in patients taking Zyban for smoking cessation. These event have occurred in patients:*

*a) with and without pre-existing psychiatric disease; some have had their psychiatric illness worsened.*

*b) In most cases, these events developed during Zyban treatment, but in others, these events developed following withdrawal of Zyban therapy.*

### **Nicotine**

The findings in this case series support a further review of the other nicotine dosage formulations for suicidal-related events.

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<sup>93</sup>This wording also needs to be incorporated into labeling for *other* bupropion products (i.e. Wellbutrin, generics).

## 7 APPENDICES

### APPENDIX 1: SIGNIFICANT CHANGE<sup>94</sup> FROM THE PAST FOR VARENICLINE (N=38); SELECTED FROM A TOTAL OF 63 CASES<sup>95</sup>

Event	ISR#	Age (yrs)	Sex	Psych hx; Psych meds	Psych disease worsened	Excerpt from report
suicide attempt	5526305	53	M	no no		Concerning attempted suicide: 'this is not a person that has EVER thought of or attempted such a thing' patient thought he was punishing himself--that he was bad--told his wife--why are you still with (married) to me? Patient has similar bad feelings and suicidal thoughts after attempt.
completed suicide	5511778	59	M	no no		During the time her father was on Chantix, they [family] never saw anything from him or had any indication why this happened. Nothing was new for her father except the Chantix.
suicide attempt	5507530	29	F	no no		Patient took on a different personality that was not known before.
suicide attempt	5449401	42	M	no no		Began talking continually about killing himself daily, since 8/28/07. he tried to kill himself by firing a 50 caliber pistol near his head, yesterday, 8/29/07.
suicidal ideation	5527862	45	F	no no		'..bouts of uncontrollable emotions and decreased clarity have made my life hell; I hope all this stops and I can resume my normal life....I don't want a cigarette..Makes me feel as though I have been traumatized with a medication into being smoke free. My children could have been parentless or I could have been a risk at work; people who know me and seen what I was going through couldn't believe it. I'm not like that person.'
suicidal ideation	5492653	50	F	no no		Began to have randomly suicidal thoughts and incredibly bad dreams; suicidal thoughts began to build...until she finally had a bizarre mental situation.....not having control over her moods, shutting down mentally, change in the way she interacted with people, Consumer has no personal or family history of suicidal thoughts
self-injurious ideation	5485254	30	F	no no		'....Became very depressed for no apparent reason and started having suicidal thoughts; I worried that I was going to hurt myself or someone else. I thought that I might go crazy and felt completely out of sorts; I quit taking the pill; about 36 hours later I felt like myself again.'
suicidal ideation	5473936	44	F	no no		(Past history): 'not an anxious person; was very on top of things, very organized and very in-control; after Chantix: unable to stop crying, could not stand anyone, feeling suicidal, had no control; was sent to crisis center.'
suicidal	5469623	33	F	no no		'I had severe depression for the first time in my life. I was

<sup>94</sup>'Significant change' means

- (1) the suicidal event(s) were a first-time occurrence for the patient, i.e. the patient had no history or remembrance of ever having experienced such events or
- (2) the patient did have a history of a psychiatric disease, but it was being adequately treated and or was felt to be under control. After taking varenicline, the pre-existing psychiatric disease worsened.

<sup>95</sup>Because varenicline had many more such reports than the other drugs (Bupropion, n=17, nicotine, n=5), it was decided to present a portion (60%; n=38) of the varenicline reports. The 38 reports are of a similar proportion of the full population, such that there are 22 (58%) for first time behavior changes and 16 (42%) for disease worsening.

Event	ISR#	Age (yrs)	Sex	Psych hx; Psych meds	Psych disease worsened	Excerpt from report
ideation						threatened with losing my job because of interaction with co-workers; broke off a two-year relationship with my boyfriend.'
suicidal ideation	5394795	35	Fe	no no		Had argument with her boyfriend and was irritated and agitated, described as screaming then she said she had suicidal thoughts which are not normal for her.
completed suicide	5491114	47	F	no yes		'Gunshot wound to the head which she did in front of her children; completely out of character for the type of person she is. While I [deceased's physician] do not know if Chantix played a role in this sudden behavior change, I feel it necessary to report.'
completed suicide	5387657	41	F	yes yes	bipolar	'There were no indications of why she [reporter was ex-wife of deceased] would have taken her own life. Diagnosed as bipolar 5-6 years ago. Was taking antidepressants--I'm not sure what--and had good control of her bipolar. My impression is that the Chantix caused severe depression which resulted in her actions.'
completed suicide	5475234		M	no unk		Started Chantix and committed suicide in (b) (6); 'no records of the patient showing any anxiety, depression, or psychological disorders in the past.'
intentional self-injury	5477086	43	F	yes yes	depression	'...Became seriously depressed. I felt like I just did not want to 'be' anymore; nobody cared about me; I was alone. I want to hurt myself. tried to hurt myself; Crying for no reason, unable to stop crying; Stressed from not knowing what is happening to me. Am I going crazy? Started drinking alcohol more often; Stopped Chantix before I became suicidal. 1998 diagnosed with Major Depression.....Been taking 37.5 mg of Paxil since with no problems.'
gun shot wound	5484816		F	yes unk		...Did not admit to any depressive symptoms; then patient shot herself in parking lot 4 days later.
completed suicide	5527925	53	M	no unk		[During last two weeks of life] '....it's almost like he was a different person; he spoke with me [son of deceased] and in a rushed panic he described <i>exactly</i> what to do and who to call if anything were to happen to him....Less than two weeks later he was dead from a self-inflicted gun shot wound to his head. He abruptly stopped driving his truck, something he had done for the past 20+ years. He unloaded his personal belongings into a rental car and headed home. He stopped and saw my brother for the first time in 5 years. He also called some friends he hadn't spoken to in 6-8 years.'
suicide attempt	5520389	58	F	yes yes	bipolar	Patient had bipolar 'all her life' which was under control with various meds (most recently duloxetine). After Chantix exposure, had deep depression, anxiety, restlessness, suicidal state. Suicide attempt by overdose of oxycodone and alprazolam Patient knows difference between nicotine withdrawal and what she experienced--they were not the same
completed suicide	5509917	30	M	unk unk		3 weeks after her son starting the medication [Chantix] he began acting odd and complaining of feeling strange and having bad dreams.
suicidal ideation	5292547	53	F	yes yes	depression	Worsening of depression and thoughts of suicide
suicidal ideation	5328998	51	F	yes yes	depression	Concerning pre-existing depression which she had for many years (and was being managed), she is aware of the signs and symptoms of what to do for them. Depression was progressing

Event	ISR#	Age (yrs)	Sex	Psych hx; Psych meds	Psych disease worsened	Excerpt from report
						to suicidal; she knew that there was a problem using the Chantix with Cymbalta. She is concerned for newly diagnosed depression patients who might use Chantix and Cymbalta concomitantly.
suicidal ideation	5527856	35	M	yes yes	depression	'I feel strongly that this behavior was not typical of me. I blew up at co-workers and was generally on a hair trigger. This week I lost any remaining control and was hospitalized. Why would a drug test exclude potential candidates due to their history of depression?'
suicidal ideation	5413087	52	F	yes yes		'She swung at her mother (who was in her late 90's) due to the extreme rage as she almost struck her and missed. She went out in the back years and she broke a weedwacker, a couple of glasses, the frame work on a couple of lamps, she threw concrete in the back yard and she took garden tools and she began stabbing chunks of wood with the garden tools to get her rage out. The rage was horrendous and it was very frightening to others. She could not communicate with anyone <i>she was a different person.</i> '
suicidal ideation	5453231	57	M	yes yes	depression	'Depression worsened to the point where he felt like he wanted to shoot himself; Chantix stopped all his endorphins that cause pleasure and happiness.'
suicidal ideation	5465454	56	F	unk unk		Suicidal thoughts from those dreams (abnormal); 'one more week and I don't know if I'd be here today'; my husband knew there was something wrong, so he kept a close eye on me.'
suicidal ideation	5466977	48	F	yes unk	depression	'My husband noticed a marked change in my mood; my depression has worsened.'
suicidal ideation	5469710	54	F	unk unk		'Although I didn't realize it that it was this medication that was affecting me until towards the end of taking it--it had serious affects on my psychological state and emotional stability. ...reacted emotionally to any challenge in my life.'
suicidal ideation	5491635	31	F	yes unk	depression	'I have previously been diagnosed with depression, but have never had vivid suicidal thoughts.'
suicidal ideation	5483678		F	unk unk		'None of these problems (depression, anxiety, suicidal thoughts) existed before she took the referenced (Chantix) medication.'
suicidal ideation	5274495	21	M	yes yes		Physician stated stated patient was not overtly depressed and believed patients' events were due to Chantix.
suicidal ideation	5520342	30	M	yes unk	depression	Suicidal thoughts; past history of depression when young (14-16 yrs); subsided with age. Patient now 30 yrs-old and has had suicidal thoughts after she stopped Chantix; 'unable to concentrate at work, unable to drive or perform my job.'
suicidal ideation	5493440	38	M	yes unk		'My confusion grew to the point where I could no longer to distinguish reality from the dream. I felt as though I was losing control of my mind for the first time in my life, suicide became an option to stop the madness; I'm afraid to go to sleep for fear of another experience.'
suicidal ideation	5501614	54	M	yes yes	bipolar	'Experienced extreme flare of his bipolar disease with severe suicidal ideation and hallucinations.'
suicidal ideation	5503402	33	F	yes yes		Patient developed suicidal thoughts which she also describes as she thought about killing herself in 2007 after starting Chantix where she was driving on the Golden Gate Bridge and she thought that looks like a good place to pull over and jump off.; she reports she has not history of depression or suicidal

Event	ISR#	Age (yrs)	Sex	Psych hx; Psych meds	Psych disease worsened	Excerpt from report
						thoughts. Within the first couple of days of taking Chantix, she noticed something was different. She was not under the care of a psychiatrist before Chantix, but was so after.
self-injurious ideation	5503884	41	F	yes yes	bipolar	'It [Chantix] seemed to block my psychiatric meds; before I realized and stopped taking it, I was a serious threat to myself and other people; I was to the point of being committed for help when I stopped taking it; it can create uncontrollable violence in a matter of a day; I stopped taking it and I slowly started to feel human again....'
suicidal ideation	5522438	43	M	yes yes	bipolar; psychosis	He noticed especially when he wasn't smoking [Chantix effective] that his personality had dramatically changed. Rather than being patient, he was quick to anger and intolerant of 'bull crap'. He is a perfectionist, but generally a patient person prior to Chantix use.
suicidal ideation	5524240		F	yes unk	bipolar	The consumer's bipolar disorder presents as depression most of the time, and she rarely has a manic episode. The consumer has been aggressive to the point that her husband called her a profanity, in 2007 after starting Chantix She states that she is having anxiety right now. Chantix made her aggressive and angry. She would "holler" at her husband for no reason.
suicidal ideation	5522389	47	F	yes unk	depression	While on Chantix she mentioned that her depression worsened and she had suicidal ideation
suicide attempt	5477018	52	F	yes yes	depression and anxiety	Was on other antidepressants/antianxiety medications at the time of using chantix. Took drug chantix for about two weeks and attempted suicide. Never had this ideation before using this drug. I almost died, was in ICU for three days and the hospital for a week. I hope doctors are aware that chantix does not mix with antidepressants. antianxiety meds. Someone needs to be aware to prevent this event happening to others. It has made a major impact on my life and my families lives;

**APPENDIX 2: SIGNIFICANT CHANGE<sup>96</sup> FROM THE PAST FOR BUPROPION;  
SUICIDE IDEATION AND SUICIDE (ATTEMPT AND COMPLETED) (N=17)**

Event	ISR #	Age Year	Sex	Psych Hx	Psych Meds <sup>97</sup>	Psych disease worsened	Excerpt from report
overdose	3122492	37	M	no	unk		Patient had no prior history of suicidal ideation; there were no other co-ingestants reported or identified.
intentional self injury	3313807	32	M	no	no		Patient is a 1 pack per day smoker who was prescribed Zyban for smoking cessation. After 1x150 mg of Zyban, he became dysphoric, 'dissociated,' and manifested suicidal ideations and used a knife to carve the words 'sick' into his arm. The patient has no history of this behavior, depression or any other prior psychiatric disorder. No other medications or alcohol was taken. Zyban was discontinued and no further details were given.
suicide attempt	3519482	--	M	no	unk		Sales rep's brother-in-law who has no history of mental problems or depression took bupropion for 8 days; [experienced] suicidal ideation and then suicide attempt.
completed suicide	4791685	51	M	no	no		No history of depression; attended church as he normally does on Sunday morning; when he returned home, he physically abused in wife and threatened to kill her; He then said 'what am I doing?' He then held a gun to his carotid area and shot himself; physician believes that Wellbutrin XL induced psychosis in patient.
intentional self injury	5062349	--	M	no	unk		2 weeks after starting bupropion, friends were telling him he had a change in his attitude; his life is ruined; people think differently of him now; Bupropion made him go crazy; he [patient] nor anyone in his family has a history of mental illness; Bupropion adverse effects made him make bad decisions, costing him his job; placed on medical leave from his job; quit his job because of his mind not being clear.
suicide completed	5082685	32	F	no	unk		Had not attempted to commit suicide in the past and had been in a good stable place in her life; this really seemed to come from nowhere.

<sup>96</sup>'Significant change' means

(1) the suicidal event(s) were a first-time occurrence for the patient, i.e. the patient had no history or remembrance of ever having experienced such events or

(2) the patient did have a history of a psychiatric disease, but it was being adequately treated and or was felt to be under control. After taking bupropion, the pre-existing psychiatric disease worsened.

<sup>97</sup>Psych medications: psychiatric related medications and or other medications labeled for suicidality.

suicidal ideation	3258509	32	F	yes	no	depression	A nurse practitioner reported that a 32 year old female received oral bupropion (Wellbutrin SR) for smoking cessation and experienced worsening of depression which was considered life-threatening.
suicidal ideation	3311864	55	M	yes	yes	psychosis	A physician's report stated that a 55 year old male with a history of psychosis and depression received Zyban tablets and the psychosis worsened. On follow up, a pharmacist reported that the patient also had a history of chronic paranoid schizophrenia and auditory hallucinations. After three weeks of Zyban therapy, the patient developed increased hallucinations and was hearing voices that told him to kill himself.
suicidal ideation	3427518	41	F	yes	yes	manic depression	After receiving bupropion, the patient experienced a reactivation of her manic depression with suicidal thoughts. The patient's medical history included manic depression, bipolar disorder, and prior use of bupropion.
suicidal ideation	3830476	46	M	no	no	chronic depression	After several days of Zyban therapy, the patient experienced extreme depression, accompanied by thoughts of suicide, panic, paranoia, and sensory changes, including difficulty in hearing and maintaining vision.
suicidal ideation	3831812	45	F	yes	yes	bipolar depression	After receiving four days of bupropion therapy, the patient reported experiencing mood swings. Per patient, bupropion interfered with topiramate, olanzapine, and clonazepam that she was taking for bipolar disorder and with her brain chemistry. She was hospitalized for six days on "suicide watch."
suicidal ideation	3904707	46	M	yes	yes	manic-depressive bipolar disorder	The patient developed a nervous and 'jittery' feeling, and subsequently developed hyperactivity, dizziness, premature ventricular contractions and shakiness. the then patient experienced a manic episode, rage, and delusional and uncontrolled impulsive behavior leading to an 'arrest for impulsive petty theft'. The patient was hospitalized for suicidal ideation after falling into deep depression.
suicidal ideation	3176184	43	F	no	unk		'I was rushed to the hospital after a day of agitation which escalated into what the doctors called a "psychotic" episode. I have little recall of this event that consisted of a series of suicidal and homicidal threats. I have no history of this type of behavior.'
suicidal ideation	3836551	25	F	no	unk		'After one dose of Zyban, I started to feel weird. I stuttered and cried while talking to her [pharmacy staff-person] - I don't normally stutter and I couldn't control my crying. By the time I started talking to that nurse

							the first time was when I started to come back to normalcy again. I was just sitting watching TV, and I remember thinking how worthless my life was and about killing myself. I kept trying to shake myself out of it, because I figured it was just because of the medicine. A nurse ended up calling me back later that day, and I told her everything. She told me to stop taking it and asked me if I'd ever felt that way without the drug. I told her no.'
suicidal ideation	3909116	28	F	no	no		2 weeks after starting bupropion, patient reports feeling 'emotional' and having regular crying fits. Patient reports having threatened to kill herself and states, 'I didn't care if I lived.' No previous indication of depression documented. Per physician, toxicity is possibly related to bupropion.
suicidal ideation	4454536	54	F	unk	no		The patient had mood changes after starting bupropion. She became tearful and had crying spells and feelings of hopelessness. She also had persistent thoughts and visions of suicidal actions, though she wouldn't have acted on them. It was not her usual state of being. She stopped the drug and everything resolved.
Suicidal Ideation	4987067	29	M	no	no		About 1 month after starting bupropion, the patient experienced lack of concentration, decreased comprehension, feelings of hopelessness, depression, suicidal thought, suicidal urges, weight loss, unable to think, decreased self care ability, fatigue in arms and legs. The patient stated that he had never been depressed in his life until taking Wellbutrin. It 'cost me life that I once knew.' The medication cost him his job, family and his visitation rights to see his children.



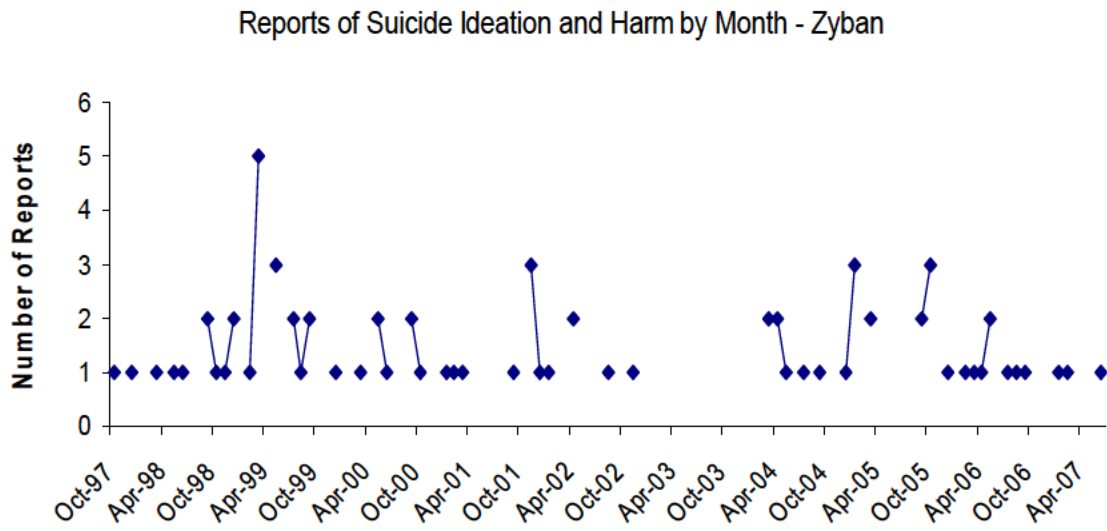
**APPENDIX 3: SIGNIFICANT CHANGE<sup>98</sup> FROM THE PAST FOR NICOTINE  
TRANSDERMAL SUICIDAL IDEATION (N=4)**

Event	ISR #	Age (yrs)	Sex	Psych Hx	Psych Meds	Psych disease worsened	Excerpt from report
Suicide Ideation	3489291	55	F	yes	yes	depression	The consumer reported that after using Nicoderm she didn't feel herself. She had awoken every morning with the back of her head tightening up. She reported that the problem started when she came off her smoking patch prior to the hospital admission but had become worse in the past five days. She had been crying incessantly, unable to do any work around the house and had become increasingly despondent with ideas of suicide.
Suicidal Ideation	4053399	39	F	yes	yes	major depression; suicide attempts	She experienced episodes of breaking into tears and having bad dreams while on nicotine patch. A few weeks later, due to stressful family issues, the patient's physician increased her Zyprexa dose. The patient subsequently experienced suicidal ideation and applied pen marks to her wrists where she would cut them. The patient stated that since starting Nicoderm, there has been an increased frequency of suicidal ideation.
Suicidal Ideation	4183560	33	unk	yes	unk	severe depression; anxiety, panic attacks	The patient became suicidal one day after discontinuation of a Nicoderm CQ 21 mg patch. It was reported that withdrawal of nicotine further aggravated the pre-existing depression.
Suicidal Ideation	4678586	43	M	yes	yes	depression; bipolar disorder, schizoaffective disorder	While stepping down to a 14 mg patch, he experienced suicidal thoughts that lasted a couple of days and relapsing depression.

<sup>98</sup>'Significant change' means

- (1) the suicidal event(s) were a first-time occurrence for the patient, i.e. the patient had no history or remembrance of ever having experienced such events or
- (2) the patient did have a history of a psychiatric disease, but it was being adequately treated and or was felt to be under control. After taking nicotine, the pre-existing psychiatric disease worsened.

#### APPENDIX 4 REPORTS OF SUICIDE IDEATION –ZYBAN



## APPENDIX 5: DRUG UTILIZATION METHODS, TABLES AND FIGURES

### Determining Setting of Use

The IMS Health, IMS National Sales Perspectives™ was used to determine the retail and non-retail channels of distribution for varenicline (Chantix®), bupropion (Zyban®, Buproban®), and transdermal nicotine patches for the most current calendar year 2007. The examination of wholesale sales data by number of extended units (tablets, individual patches, etc.) sold for year 2007 indicate that the majority of sales were directed toward the outpatient retail pharmacy settings (chain, independent, food stores with pharmacies) for these products. The outpatient retail pharmacy setting accounted for approximately 88% of distribution for Chantix®, 69% for bupropion products, and 63% for transdermal nicotine patches (data not shown).<sup>99</sup> Non-retail pharmacies such as hospitals and clinics accounted for nearly 8% of distribution for Chantix® and nearly a quarter of distribution for bupropion products and transdermal nicotine patches, each. Mail service pharmacies accounted for approximately 4%, 7% and 11% of distribution Chantix®, bupropion products, and transdermal nicotine patches, respectively. We examined outpatient utilization patterns. Mail order data are not included in this analysis.

### Data Sources Used

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (see Appendix 6 for full database descriptions).

Because a large proportion of smoking cessation products are available as over-the-counter (OTC) as well as prescription, we examined wholesale distribution patterns using the IMS Health, IMS National Sales Perspectives™ to gain a comprehensive view of all products in the USC5 Class 69000 “Smoking Deterrents”. Using this database, total sales volume in extended units (individual tablets, patches, etc.) for prescription and OTC smoking deterrent products were examined for years 2003 through 2007.

In addition, total dispensed prescriptions for products in the USC5 Class 69000 “Smoking Deterrents” were examined using the Verispan, LLC: Vector One®: National (VONA) for calendar years 1991 through 2007. We also examined number of patients who received a prescription for these products in the outpatient setting using Verispan, LLC: Vector One®: Total Patient Tracker (TPT) by year from 2002 to 2007, and also cumulatively from year 2002 to 2007.

Concurrent psychotropic drug use with Chantix® or bupropion (Buproban®, Zyban®) products were also examined using the Verispan, Vector One®: Concurrency (VOCON) tool. An episode of concurrency is identified when the days supply for a dispensed prescription in Base Group (Chantix® or bupropion) overlaps with the days supply for a dispensed prescription in Concurrent Groups (Antidepressants-Antipsychotics-Anxiolytics). The days supply is calculated by adding the number of *therapy days* to the time of prescription dispensing. The number of *therapy days* is estimated by dividing the number of tablets or capsules dispensed by the number of tablets or capsules consumed per day. A 50% grace period is allowed for the days supply time window to adjust for delays in prescription filling. Only years 2006 and 2007 were analyzed for concurrent use with Chantix® or bupropion (Buproban®, Zyban®) products.

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<sup>99</sup> IMS Health, IMS National Sales Perspectives™, Data extracted 3-5-08. File: 0803smok.dvr

## Products Included

Products in the USC5 69000 Smoking Deterrents Class include nicotine products, varenicline (Chantix<sup>®</sup>), and bupropion (Zyban<sup>®</sup>, Buproban<sup>®</sup>).

For the concurrency analysis, two sets of reports were generated and analyzed for concurrency between varenicline (Chantix<sup>®</sup>) or bupropion (Zyban<sup>®</sup>, Buproban<sup>®</sup>) and psychotropic drug products. Psychotropic drug products were further broken down by the following markets: antidepressants, antipsychotics, and anxiolytics.

Base Group:

Scenario A: varenicline (Chantix<sup>®</sup>)

Scenario B: bupropion (Zyban<sup>®</sup>, Buproban<sup>®</sup>)

Concurrent Group:

ANTIPSYCHOTICS		
USC 64110	Phenothiazine Derivatives	CHLORPROMAZINE HCL, FLUPHENAZ DE, MELLARIL, MELLARIL-S, PERMITIL, PERPHENAZINE, PRO-MED, PROLIXIN, PROLIXIN-DEC, PROLIXIN DECANOATE, PROLIXIN ENANTHATE, PROMAZINE, SERENTIL, SPARINE, STELAZINE, THIORIDAZINE, THORAZINE, TRIFLUOPERAZINE, TRILAFON, VESPRIN
USC 64190	Antipsychotics Other	ABILIFY, CLOZARIL, CYTADREN, FAZACLO, GEODON IM, GEODON ORAL, HALDOL DECANOATE, HALOPERIDOL, HALOPERIDOL DECANOAT, HALOPERIDOL LACTATE, INVEGA, LOXAPINE, LOXITANE, LOXITANE C, LOXITANE IM, MOBAN, NAVANE, ORAP, RISPERDAL, RISPERDAL CONSTA, RISPERDAL M-TAB, SEROQUEL, SEROQUEL XR, THIOTHIXENE, ZYPREXA, ZYPREXA ZYDIS
USC 64900	Miscellaneous	ANTABUSE, DISULFIRAM
ANTIDEPRESSANTS		
USC 64310	Tricyclic/Tetracyclic Antidepressants	ADAPIN, AMITRIPTYLINE, AMOXAPINE, ANAFRANIL, ASENDIN, AVENTYL HCL, CLOMIPRAMINE HCL, DESIPRAMINE, DOXEPIN, ELAVIL, ENDEP, IMIPRAMINE HCL, LUDIOMIL, MAPROTILINE, MIRTAZAPINE, NORPRAMIN, NORTRIPTYLINE, PAMELOR, PROTRIPTYLINE, REMERON, REMERON SOLTAB, SINEQUAN, SURMONTIL, THSC DESIPRM, TOFRANIL, TOFRANIL PM, TRIMIPRAMINE, VANATRIP, VIVACTIL
USC 64320	MAO Inhibitors	EMSAM, MARPLAN, NARDIL, PARNATE, TRANLYCYPROMINE SULFATE

USC 64330	New Generation Antidepressants	APPBUTAMONE, APPBUTAMONE-D, BUDEPRION SR, BUDEPRION XL, BUPROPION, BUPROPION ER, BUPROPION HCL SR, BUPROPION SR, BUPROPION XL, DESYREL, DESYREL DIVIDOSE, NEFAZODONE HCL, SERZONE, TRAZAMINE, TRAZODONE HCL, WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL
USC 64340	SSRI's	CELEXA, CITALOPRAM HBR, FLUOXETINE, FLUVOXAMINE, GABOXETINE, LEXAPRO, LUVOX, LUVOX CR, PAROXETINE, PAXIL, PAXIL CR, PEXEVA, PROZAC, PROZAC WEEKLY, RAPIFLUX, SARAFEM, SENTROXATINE, SERTRALINE, ZOLOFT
USC 64350	SNRI's	CYMBALTA, EFFEXOR, EFFEXOR XR, PRISTIQ, VENLAFAXINE
USC 64380	Combination Antidepressants	AMITRIPTYLINE/CHLORDIAZEP, CDP/AMITRIP, CHLORDIAZ/AMITRIP, DUO-VIL, ETRAFON, ETRAFON 2-10, ETRAFON 2-25, ETRAFON FORTE 4-25, LIMBITROL, LIMBITROL DS, PERPHENAZN/AMITRIP, REXIN, SYMBYAX, TRIAVIL

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#### ANXIOLYTICS

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USC 64610	Benzodiazepines	ALPRAZOLAM, ALPRAZOLAM ER, ALPRAZOLAM INTENSOL, ATIVAN, CHLORDIAZEPOXIDE HCL, CLORAZEPATE DIPOT, D-VAL, DI TRAN, DIAZEPAM, DIZAC, GABAZOLAMINE, GEN-XENE, H-TRAN, LIBRITABS, LIBRIUM, LIPOXIDE, LORAZEPAM, MIDAZOLAM, MIDAZOLAM 0.9% NACL, NIRAVAM, OXAZEPAM, PAXIPAM, SERAX, SPAZ-5, THSC DIAZEPM, THSC LORAZEP, TRANXENE SD, TRANXENE T, TRANXENE T-TAB, VALIUM, VERSED, XANAX, XANAX XR
USC 64690	Antianxiety Other	ANX, ATARAX, ATAZINE, BUSPAR, BUSPAR DIVIDOSE, BUSPAR ONE MTH SPPLY, BUSPIRONE HCL, HYDROXYZINE, HYDROXYZINE PAMOATE, HYZINE, MB, MEPROBAMATE, MILTOWN, NEUCALM, REZINE, THSC HYDRXYZ, VANSPAR, VISTACOT, VISTAJECT, VISTARIL, VISTARIL IM, VISTAZINE

Table 1: Total number of extended units (patches, tablets, gum, etc) from manufacturer to wholesale retail and non-retail distribution channels, Year 2003 through 2007

	2003		2004		2005		2006		2007	
	N (000)	%	N (000)	%	N (000)	%	N (000)	%	N (000)	%
<b>69000 SMOKING DETERRENTS</b>	311,418	100.0	321,397	100.0	309,132	100.0	368,684	100.0	684,394	100.0
VARENICLINE		0.0		0.0		0.0	55,790	15.1	413,761	60.5
TABS COATED REGULAR ORD		0.0		0.0		0.0	55,790	100.0	413,761	100.0
<b>NICOTINE</b>	262,801	84.4	272,097	84.7	255,323	82.6	260,982	70.8	216,822	31.7
ORAL SOLD REG CHEWAB	164,467	62.6	139,206	51.2	124,106	48.6	113,710	43.6	105,314	48.6
PAD/PATCH TRANSDERMAL	40,398	15.4	44,697	16.4	50,740	19.9	50,617	19.4	44,848	20.7
LOZENGE REGULAR ORDINAR	16,595	6.3	20,307	7.5	20,861	8.2	45,287	17.4	26,790	12.4
INHALNT SPRY SYSTM C USE	23,674	9.0	41,604	15.3	42,711	16.7	37,375	14.3	22,239	10.3
ORAL SOLD REG ORDIN	16,319	6.2	24,657	9.1	15,141	5.9	12,150	4.7	15,965	7.4
NASAL SPRAY SYSTM C	1,348	0.5	1,626	0.6	1,764	0.7	1,844	0.7	1,665	0.8
<b>NIKETHAMIDE</b>	8,924	2.9	15,026	4.7	26,431	8.5	28,718	7.8	40,716	5.9
ORAL SOLD REG CHEWAB	8,924	100.0	15,026	100.0	26,431	100.0	28,718	100.0	40,716	100.0
<b>BUPROPION</b>	39,693	12.7	34,274	10.7	27,379	8.9	23,193	6.3	13,095	1.9
TABS COATED LG/ACT ORD	39,693	100.0	34,274	100.0	27,379	100.0	23,193	100.0	13,095	100.0

Source: IMS National Sales Perspectives: Retail, IMS National Sales Perspectives: Non-Ret. Extracted 3-08. File: 0803nict.dvr

Table 2: Total number of dispensed prescriptions for smoking deterrent products, USC5 69000, from U.S. outpatient retail pharmacies, Years 1991 - 2007

	1991		1992		1993		1994		1995	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%	N	%	N	%
<b>69000 SMOKING DETERRENTS</b>	3,487,857	100.0%	10,897,783	100.0%	5,874,675	100.0%	4,554,763	100.0%	4,371,866	100.0%
Varenicline	--	--	--	--	--	--	--	--	--	--
Chantix	--	--	--	--	--	--	--	--	--	--
Nicotine Transdermal Patch	15,512	0.4%	8,862,463	81.3%	4,331,667	73.7%	3,008,975	66.1%	2,792,116	63.9%
Nicotine Transdermal	--	--	--	--	--	--	--	--	--	--
Nicoderm CQ	--	--	--	--	--	--	--	--	--	--
Nicoderm	38	0.2%	3,687,083	41.6%	1,853,210	42.8%	1,556,571	51.7%	1,618,655	58.0%
Habitrol	15,474	99.8%	4,153,488	46.9%	1,469,275	33.9%	897,129	29.8%	743,145	26.6%
Nicotrol TD	--	--	130,850	1.5%	522,848	12.1%	326,460	10.8%	282,949	10.1%
ProStep	--	--	891,042	10.1%	486,334	11.2%	228,815	7.6%	147,367	5.3%
Nicotine Inhalant, Other	--	--	--	--	--	--	--	--	--	--
Nicotrol Inhaler	--	--	--	--	--	--	--	--	--	--
Bupropion	--	--	--	--	--	--	--	--	--	--
Buprobán	--	--	--	--	--	--	--	--	--	--
Zyban	--	--	--	--	--	--	--	--	--	--
Nicotine Nasal Spray	--	--	--	--	--	--	--	--	--	--
Nicotrol NS	--	--	--	--	--	--	--	--	--	--
Nicotrol Inhaler	--	--	--	--	--	--	--	--	--	--
Nicotrol NS	--	--	--	--	--	--	--	--	--	--
Nicotine Chewing Gum	3,472,345	99.6%	2,035,320	18.7%	1,543,008	26.3%	1,545,788	33.9%	1,579,750	36.1%
Nicorette	3,472,251	100.0%	2,035,290	100.0%	1,526,610	98.9%	1,484,219	96.0%	1,471,068	93.1%
Nicorette DS	94	0.0%	30	0.0%	16,398	1.1%	61,569	4.0%	108,682	6.9%

Source: Verispan, Vector One®: National (VONA), 1991 - 2007. File: VONA 2007-2425 3-6-08 Smoking Cess TRx.xls

Table 2 continued: Total number of dispensed prescriptions for smoking deterrent products, USC5 69000, from U.S. outpatient retail pharmacies, Years 1991 - 2007

	1996		1997		1998		1999		2000	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%	N	%	N	%
<b>69000 SMOKING DETERRENTS</b>	2,793,246	100.0%	1,287,029	100.0%	2,980,632	100.0%	2,577,422	100.0%	2,112,292	100.0%
Varenicline	--	--	--	--	--	--	--	--	--	--
Chantix	--	--	--	--	--	--	--	--	--	--
Nicotine Transdermal Patch	2,123,614	76.0%	428,335	33.3%	272,408	9.1%	309,594	12.0%	299,943	14.2%
Nicotine Transdermal	--	--	--	--	28,684	10.5%	106,082	34.3%	179,851	60.0%
Nicoderm CQ	--	--	--	--	--	--	55,901	18.1%	75,383	25.1%
Nicoderm	1,210,303	57.0%	70,940	16.6%	24,963	9.2%	17,469	5.6%	9,432	3.1%
Habitrol	637,036	30.0%	328,042	76.6%	205,622	75.5%	127,660	41.2%	34,744	11.6%
Nicotrol TD	194,144	9.1%	7,660	1.8%	1,651	0.6%	1,110	0.4%	346	0.1%
ProStep	82,131	3.9%	21,693	5.1%	11,488	4.2%	1,372	0.4%	187	0.1%
Nicotine Inhalant, Other	--	--	10	0.0%	146,798	4.9%	504,622	19.6%	340,834	16.1%
Nicotrol Inhaler	--	--	10	100.0%	146,798	100.0%	504,622	100.0%	340,834	100.0%
Bupropion	--	--	696,260	54.1%	2,433,995	81.7%	1,663,688	64.5%	1,389,753	65.8%
Buprobán	--	--	--	--	--	--	--	--	--	--
Zyban	--	--	696,260	100.0%	2,433,995	100.0%	1,663,688	100.0%	1,389,753	100.0%
Nicotine Nasal Spray	39,334	1.4%	145,771	11.3%	119,423	4.0%	95,279	3.7%	79,720	3.8%
Nicotrol NS	39,334	100.0%	145,771	100.0%	119,423	100.0%	95,279	100.0%	79,720	100.0%
Nicotrol Inhaler	--	--	--	--	--	--	--	--	--	--
Nicotrol NS	--	--	--	--	--	--	--	--	--	--
Nicotine Chewing Gum	630,298	22.6%	16,653	1.3%	8,008	0.3%	4,239	0.2%	2,042	0.1%
Nicorette	573,852	91.0%	13,019	78.2%	6,211	77.6%	3,207	75.7%	1,551	76.0%
Nicorette DS	56,446	9.0%	3,634	21.8%	1,797	22.4%	1,032	24.3%	491	24.0%

Source: Verispan, Vector One®: National (VONA), 1991 - 2007. File: VONA 2007-2425 3-6-08 Smoking Cess TRx.xls

Table 2 continued: Total number of dispensed prescriptions for smoking deterrent products, USC5 69000, from U.S. outpatient retail pharmacies, Years 1991 - 2007

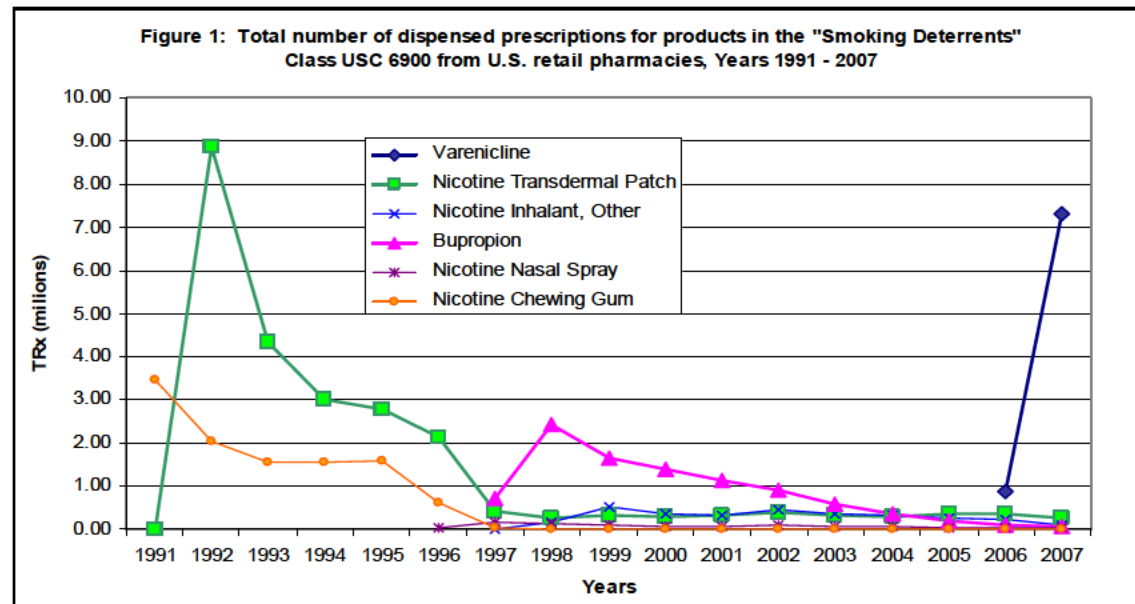
	2001		2002		2003		2004		2005	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%	N	%	N	%
<b>69000 SMOKING DETERRENTS</b>	1,875,177	100.0%	1,806,383	100.0%	1,330,626	100.0%	1,027,630	100.0%	846,306	100.0%
Varenicline	--	--	--	--	--	--	--	--	--	--
Chantix	--	--	--	--	--	--	--	--	--	--
Nicotine Transdermal Patch	321,859	17.2%	378,101	20.9%	310,148	23.3%	288,584	28.1%	348,862	41.2%
Nicotine Transdermal	239,174	74.3%	293,169	77.5%	244,047	78.7%	219,201	76.0%	277,874	79.7%
Nicoderm CQ	73,130	22.7%	79,092	20.9%	63,141	20.4%	68,117	23.6%	69,798	20.0%
Nicoderm	5,728	1.8%	4,307	1.1%	2,107	0.7%	1,024	0.4%	1,051	0.3%
Habitrol	3,486	1.1%	1,395	0.4%	718	0.2%	173	0.1%	89	0.0%
Nicotrol TD	288	0.1%	136	0.0%	123	0.0%	66	0.0%	50	0.0%
ProStep	53	0.0%	2	0.0%	12	0.0%	3	0.0%	--	--
Nicotine Inhalant, Other	335,691	17.9%	437,515	24.2%	355,885	26.7%	322,816	31.4%	257,712	30.5%
Nicotrol Inhaler	335,691	100.0%	437,515	100.0%	355,885	100.0%	322,816	100.0%	257,712	100.0%
Bupropion	1,144,038	61.0%	903,305	50.0%	595,132	44.7%	361,532	35.2%	195,532	23.1%
Buprobán	--	--	--	--	--	--	53,619	14.8%	140,951	72.1%
Zyban	1,144,038	100.0%	903,305	100.0%	595,132	100.0%	307,913	85.2%	54,581	27.9%
Nicotine Nasal Spray	72,418	3.9%	87,017	4.8%	69,321	5.2%	54,451	5.3%	44,082	5.2%
Nicotrol NS	72,418	100.0%	87,017	100.0%	69,321	100.0%	54,451	100.0%	39,882	90.5%
Nicotrol Inhaler	--	--	--	--	--	--	--	--	4,200	9.5%
Nicotrol NS	--	--	--	--	--	--	--	--	--	--
Nicotine Chewing Gum	1,171	0.1%	445	0.0%	140	0.0%	247	0.0%	118	0.0%
Nicorette	849	72.5%	395	88.8%	83	59.3%	220	89.1%	100	84.7%
Nicorette DS	322	27.5%	50	11.2%	57	40.7%	27	10.9%	18	15.3%

Source: Verispan, Vector One®: National (VONA), 1991 - 2007. File: VONA 2007-2425 3-6-08 Smoking Cess TRx.xls

Table 2 continued: Total number of dispensed prescriptions for smoking deterrent products, USC5 69000, from U.S. outpatient retail pharmacies, Years 1991 - 2007

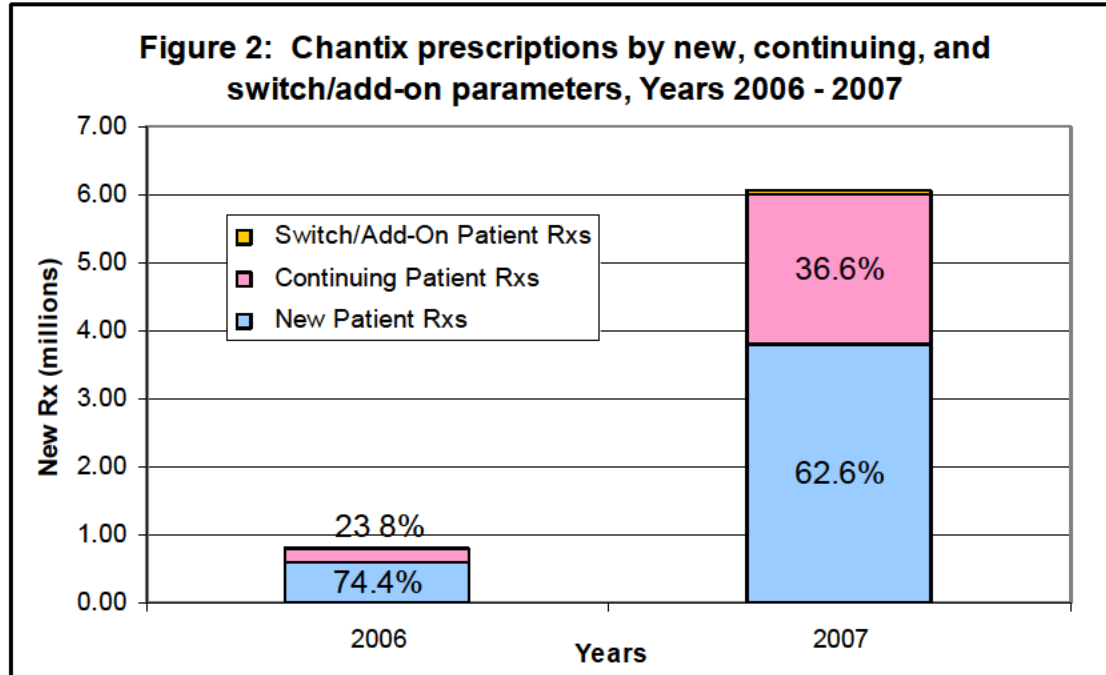
	2006		2007		1/1991-12/2007	
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share
	N	%	N	%	N	%
<b>69000 SMOKING DETERRENTS</b>	1,609,179	100.0%	7,784,891	100.0%	57,217,757	100.0%
<b>Varenicline</b>	861,860	53.6%	7,302,455	93.8%	8,164,315	14.3%
Chantix	861,860	100.0%	7,302,455	100.0%	8,164,315	100.0%
<b>Nicotine Transdermal Patch</b>	369,623	23.0%	271,931	3.5%	24,733,735	43.2%
Nicotine Transdermal	326,677	88.4%	256,299	94.3%	2,171,058	8.8%
Nicoderm CQ	42,181	11.4%	15,120	5.6%	541,863	2.2%
Nicoderm	633	0.2%	448	0.2%	10,063,962	40.7%
Habitrol	106	0.0%	53	0.0%	8,617,635	34.8%
Nicotrol TD	26	0.0%	11	0.0%	1,468,718	5.9%
ProStep	--	--	--	--	1,870,499	7.6%
<b>Nicotine Inhalant, Other</b>	216,932	13.5%	112,948	1.5%	3,031,763	5.3%
Nicotrol Inhaler	216,932	100.0%	112,948	100.0%	3,031,763	100.0%
<b>Bupropion</b>	113,140	7.0%	59,399	0.8%	9,555,774	16.7%
Buproban	87,323	77.2%	51,005	85.9%	332,898	3.5%
Zyban	25,817	22.8%	8,394	14.1%	9,222,876	96.5%
<b>Nicotine Nasal Spray</b>	47,540	3.0%	38,030	0.5%	892,386	1.6%
Nicotrol NS	41,978	88.3%	35,802	94.1%	880,396	98.7%
Nicotrol Inhaler	5,562	11.7%	373	1.0%	10,135	1.1%
Nicotrol NS	--	--	1,855	4.9%	1,855	0.2%
<b>Nicotine Chewing Gum</b>	84	0.0%	128	0.0%	10,839,784	18.9%
Nicorette	79	94.0%	112	87.5%	10,589,116	97.7%
Nicorette DS	5	6.0%	16	12.5%	250,668	2.3%

Source: Verispan, Vector One®: National (VONA), 1991 - 2007. File: VONA 2007-2425 3-6-08 Smoking Cess TRx.xls



Source: Verispan, Vector One®: National (VONA), 1991 - 2007. File: VONA 2007-2425 3-6-08 Smoking Cess TRx.xls



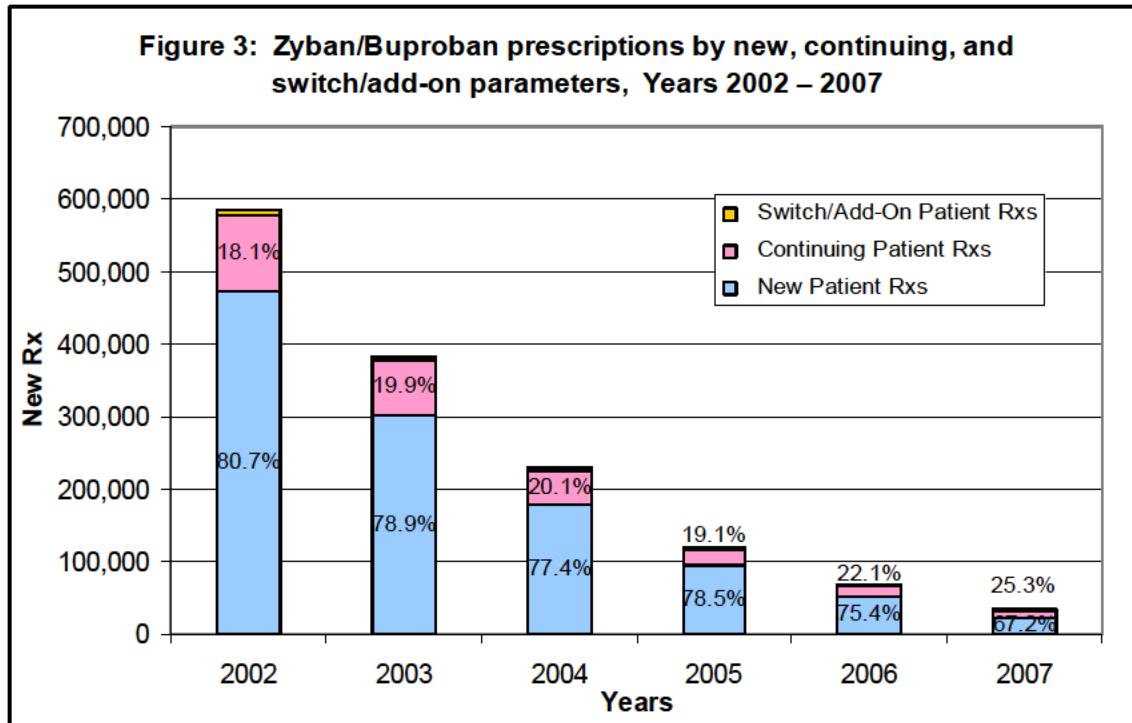


Source: Verispan, LLC. Vector One®: National. Extracted March 2008. File: VONA 2007-2425 3-6-08 Chantix RxType.qry

**Table 3: Projected number of new prescriptions switched from or added-on to Chantix in U.S. retail pharmacies, Years 2006 - 2007**

	2006		2007	
	Retail NRx	Share	Retail NRx	Share
	Swt/Ad Pt	%	Swt/Ad Pt	%
<b>Chantix Switch/Add-On From</b>	11,943	100.0%	37,038	100.0%
Nicotine Transdermal	4,100	34.3%	19,059	51.5%
Nicotrol Inhaler	4,922	41.2%	9,802	26.5%
Buproban	1,473	12.3%	4,119	11.1%
Nicoderm CQ	486	4.1%	1,540	4.2%
Nicotrol NS	392	3.3%	1,441	3.9%
Zyban	540	4.5%	983	2.7%
Nicoderm	20	0.2%	77	0.2%
Habitrol	10	0.1%	13	0.0%
Nicotrol TD	--	--	2	0.0%
Nicorette	--	--	2	0.0%

Source: Verispan, LLC. Vector One®: National. Extracted March 2008. File: VONA 2007-2425 3-6-08 Chantix PriorRx.qry



Source: Verispan, LLC. Vector One®: National. Extracted March 2008. File: VONA 2007-2425 3-6-08 zyban RxType.xls

**Table 4: Projected number of new prescriptions switched from or added-on to Zyban/Buproban in U.S. retail pharmacies, Years 2002 - 2007**

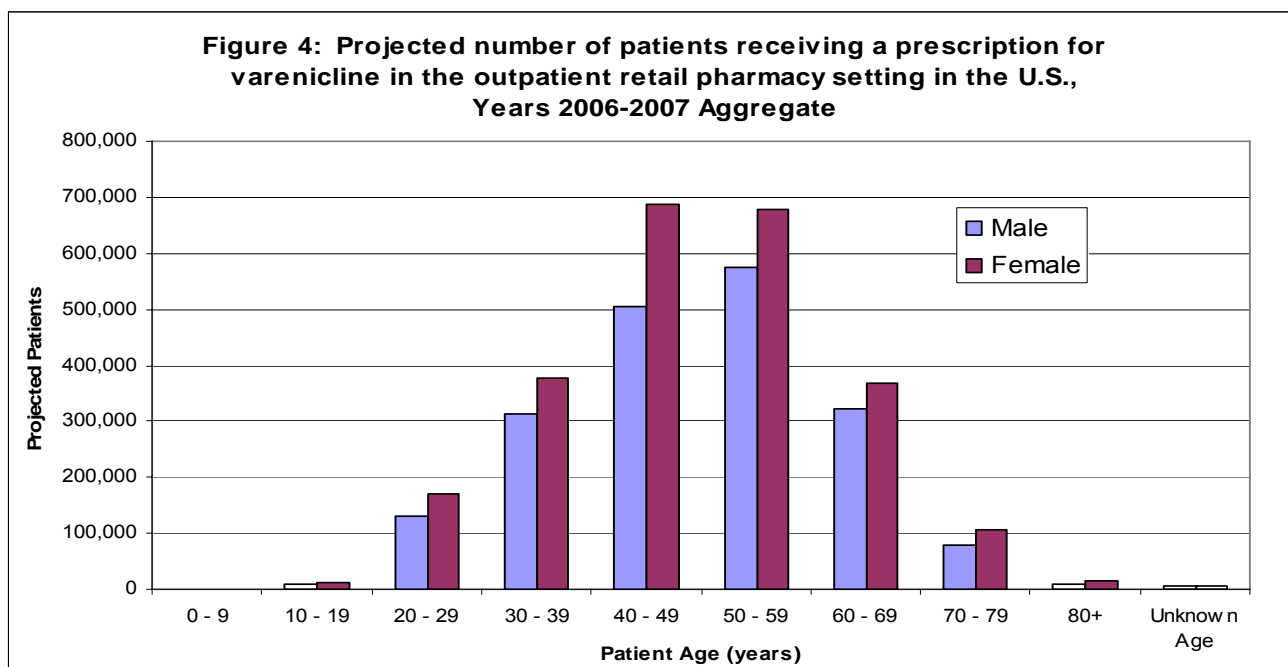
	2002		2003		2004		2005		2006		2007	
	Retail NRx Swt/Ad Pt	Share %	Retail NRx Swt/Ad Pt	Share %	Retail NRx Swt/Ad Pt	Share %	Retail NRx Swt/Ad Pt	Share %	Retail NRx Swt/Ad Pt	Share %	Retail NRx Swt/Ad Pt	Share %
<b>Bupropion Switch/Add-On From</b>	6,439	100.0%	4,208	100.0%	5,225	100.0%	2,497	100.0%	1,451	100.0%	2,265	100.0%
<b>Chantix</b>	--	--	--	--	--	--	--	--	193	13.3%	1,839	81.2%
<b>Bupropion</b>	--	--	--	--	3,004	57.5%	1,478	59.2%	617	42.5%	192	8.5%
<b>Nicotine Transdermal</b>	2,586	40.2%	1,936	46.0%	864	16.5%	491	19.7%	309	21.3%	166	7.3%
<b>Nicotrol Inhaler</b>	2,801	43.5%	1,778	42.3%	1,061	20.3%	422	16.9%	241	16.6%	55	2.4%
<b>Nicotrol NS</b>	309	4.8%	142	3.4%	81	1.6%	12	0.5%	21	1.4%	9	0.4%
<b>Nicoderm CQ</b>	605	9.4%	320	7.6%	215	4.1%	94	3.8%	68	4.7%	4	0.2%
<b>Nicorette</b>	5	0.1%	3	0.1%	--	--	--	--	--	--	--	--
<b>Nicoderm</b>	96	1.5%	29	0.7%	--	--	--	--	2	0.1%	--	--
<b>Habitrol</b>	37	0.6%	--	--	--	--	--	--	--	--	--	--

Source: Verispan, LLC. Vector One®: National. Extracted March 2008. File: VONA 2007-2425 3-6-08 zyban PriorRx.qry

**Table 5: Total number of patients receiving a prescription for varenicline (Chantix®) in U.S. outpatient retail pharmacies, Years 2006 - 2007**

Custom Age Group	Year 2006				Year 2007				Aggregate Years 2006 - 2007			
	Projected Patient Count	Total Patient Share	Male Patient	Female Patient	Projected Patient Count	Total Patient Share	Male Patient	Female Patient	Projected Patient Count	Total Patient Share	Male Patient	Female Patient
Grand Total	600,663	100.0%	268,194	331,309	3,975,048	100.0%	1,762,792	2,200,258	4,325,324	100.0%	1,923,640	2,389,164
0 - 9	283	0.0%	184	99	2,034	0.1%	1,041	970	2,264	0.1%	1,193	1,049
10 - 19	1,841	0.3%	865	961	19,181	0.5%	9,153	9,881	20,722	0.5%	9,872	10,691
20 - 29	27,660	4.6%	11,962	15,639	283,880	7.1%	123,465	159,256	303,915	7.0%	132,203	170,516
30 - 39	77,274	12.9%	34,149	43,033	641,835	16.1%	289,679	350,581	691,762	16.0%	312,163	377,982
40 - 49	162,753	27.1%	67,347	95,263	1,095,357	27.6%	462,376	631,572	1,193,031	27.6%	504,217	687,334
50 - 59	187,012	31.1%	86,869	99,992	1,147,961	28.9%	523,573	623,344	1,253,120	29.0%	574,280	677,731
60 - 69	110,747	18.4%	52,406	58,232	626,681	15.8%	290,378	335,900	690,559	16.0%	321,141	368,953
70 - 79	29,776	5.0%	13,233	16,514	165,911	4.2%	69,905	95,892	184,820	4.3%	78,406	106,284
80+	3,308	0.6%	1,307	2,001	20,173	0.5%	7,343	12,805	22,701	0.5%	8,327	14,347
Unknown Age	2,227	0.4%	859	718	19,444	0.5%	4,603	6,339	21,702	0.5%	5,477	7,042

Verispan, Vector One®: Total Patient Tracker. Years 2006 - 2007. Extracted March 2008. File: TPT 2007-2425 Chantix AgeGender Aggregate May06-Dec07 3-6-08.xls, TPT 2007-2425 Chantix AgeGender May06-Dec07 3-6-08.xls



Verispan, Vector One®: Total Patient Tracker. Years 2006 - 2007. Extracted March 2008. File: TPT 2007-2425 Chantix AgeGender Aggregate May06-Dec07 3-6-08.xls

**Table 6: Total number of patients receiving a prescription for bupropion products (Zyban®, Buproban®) in U.S. outpatient retail pharmacies, Years 2002 - 2007**

Custom Age Group	Year 2002				Year 2003				Year 2004			
	Projected Patient Count	Total Patient Share	Male Patient	Female Patient	Projected Patient Count	Total Patient Share	Male Patient	Female Patient	Projected Patient Count	Total Patient Share	Male Patient	Female Patient
<b>Grand Total</b>	<b>561,293</b>	<b>100.0%</b>	<b>273,421</b>	<b>287,893</b>	<b>377,739</b>	<b>100.0%</b>	<b>186,277</b>	<b>190,668</b>	<b>228,814</b>	<b>100.0%</b>	<b>112,686</b>	<b>115,077</b>
<b>0 - 9</b>	604	0.1%	355	251	419	0.1%	253	167	162	0.1%	115	46
<b>10 - 19</b>	5,160	0.9%	2,477	2,684	3,476	0.9%	1,702	1,769	1,651	0.7%	894	738
<b>20 - 29</b>	60,825	10.8%	27,105	33,720	40,529	10.7%	18,090	22,370	22,839	10.0%	10,150	12,656
<b>30 - 39</b>	122,333	21.8%	58,618	63,716	78,617	20.8%	37,956	40,459	45,838	20.0%	22,271	23,495
<b>40 - 49</b>	168,573	30.0%	81,930	86,654	111,102	29.4%	54,811	56,099	66,985	29.3%	32,815	33,966
<b>50 - 59</b>	132,370	23.6%	68,349	64,019	90,320	23.9%	47,643	42,535	56,929	24.9%	30,263	26,594
<b>60 - 69</b>	58,506	10.4%	29,175	29,344	42,607	11.3%	21,227	21,307	26,655	11.6%	13,205	13,362
<b>70 - 79</b>	15,612	2.8%	6,795	8,818	11,265	3.0%	5,012	6,238	7,228	3.2%	3,037	4,149
<b>80+</b>	2,097	0.4%	894	1,204	1,459	0.4%	584	874	943	0.4%	409	541
<b>Unknown Age</b>	53	0.0%	17	36	1,680	0.4%	670	857	1,170	0.5%	565	194

Verispan, Vector One®: Total Patient Tracker. Years 2002 - 2007. Extracted March 2008. File: TPT 2007-2425 Bupropion AgeGender Y02-07 3-8-08.xls, TPT 2007-2425 Bupropion AgeGender Aggregate 02-07 3-8-08.xls

**Table 6 cont': Total number of patients receiving a prescription for bupropion products (Zyban®, Buproban®) in U.S. outpatient retail pharmacies, Years 2002 - 2007**

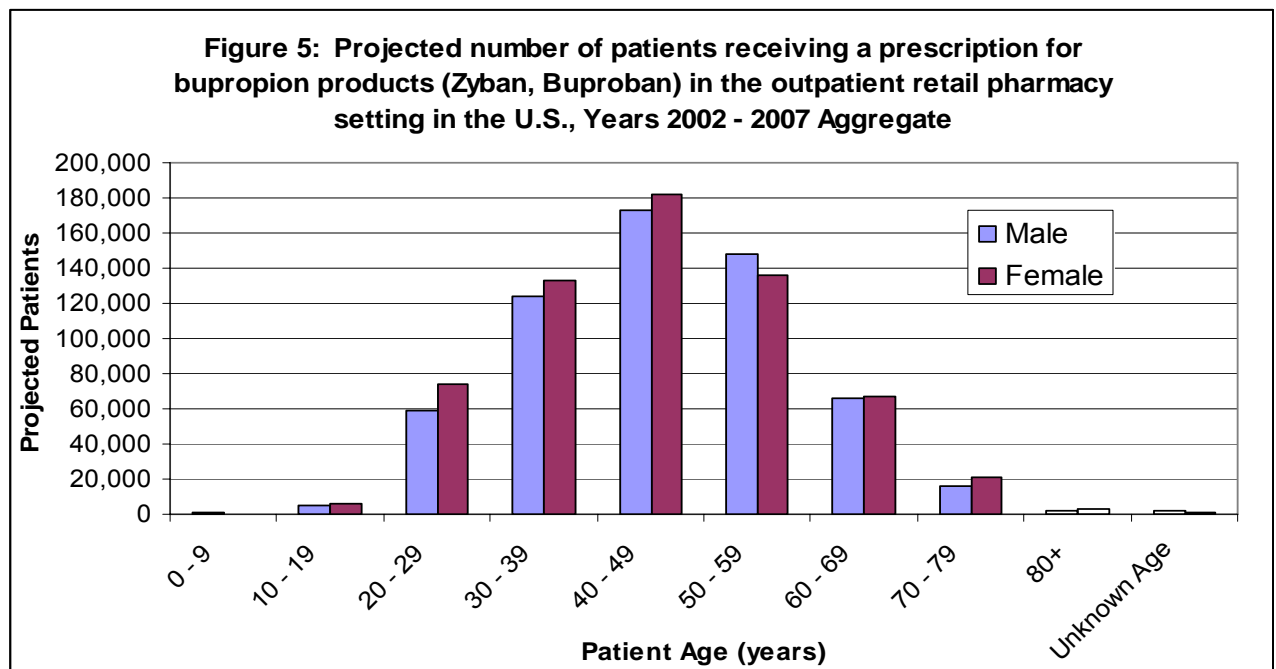
Custom Age Group	Year 2005				Year 2006				Year 2007			
	Projected Patient Count	Total Patient Share	Male Patient	Female Patient	Projected Patient Count	Total Patient Share	Male Patient	Female Patient	Projected Patient Count	Total Patient Share	Male Patient	Female Patient
<b>Grand Total</b>	<b>120,955</b>	<b>100.0%</b>	<b>57,396</b>	<b>62,981</b>	<b>67,957</b>	<b>100.0%</b>	<b>32,677</b>	<b>35,067</b>	<b>33,926</b>	<b>100.0%</b>	<b>14,921</b>	<b>18,855</b>
<b>0 - 9</b>	38	0.0%	31	5	49	0.1%	31	18	16	0.0%	8	8
<b>10 - 19</b>	768	0.6%	346	400	430	0.6%	198	216	361	1.1%	174	182
<b>20 - 29</b>	10,947	9.1%	4,808	6,091	6,306	9.3%	2,813	3,462	3,129	9.2%	1,201	1,900
<b>30 - 39</b>	23,434	19.4%	11,038	12,319	12,553	18.5%	6,298	6,226	6,708	19.8%	3,016	3,652
<b>40 - 49</b>	34,954	28.9%	16,101	18,771	18,967	27.9%	8,965	9,977	8,963	26.4%	3,938	5,009
<b>50 - 59</b>	31,439	26.0%	16,030	15,326	17,319	25.5%	8,581	8,707	8,428	24.8%	3,879	4,540
<b>60 - 69</b>	14,957	12.4%	7,327	7,561	9,710	14.3%	4,729	4,967	4,862	14.3%	2,176	2,681
<b>70 - 79</b>	4,335	3.6%	1,814	2,485	2,707	4.0%	1,126	1,561	1,513	4.5%	598	902
<b>80+</b>	498	0.4%	131	366	364	0.5%	135	230	219	0.6%	79	142
<b>Unknown Age</b>	771	0.6%	259	232	344	0.5%	202	55	95	0.3%	34	33

Verispan, Vector One®: Total Patient Tracker. Years 2002 - 2007. Extracted March 2008. File: TPT 2007-2425 Bupropion AgeGender Y02-07 3-8-08.xls, TPT 2007-2425 Bupropion AgeGender Aggregate 02-07 3-8-08.xls

**Table 6 cont': Total number of patients receiving a prescription for bupropion products (Zyban®, Buproban®) in U.S. outpatient retail pharmacies, Years 2002 - 2007**

Custom Age Group	Aggregate Years 2002 - 2007			
	Projected Patient Count	Total Patient Share	Male Patient	Female Patient
<b>Grand Total</b>	<b>1,196,444</b>	<b>100.0%</b>	<b>583,593</b>	<b>610,468</b>
<b>0 - 9</b>	1,225	0.1%	766	460
<b>10 - 19</b>	11,289	0.9%	5,495	5,727
<b>20 - 29</b>	132,749	11.1%	58,937	73,620
<b>30 - 39</b>	257,744	21.5%	123,930	133,443
<b>40 - 49</b>	355,683	29.7%	172,834	182,414
<b>50 - 59</b>	285,029	23.8%	148,404	136,336
<b>60 - 69</b>	133,490	11.2%	66,354	66,929
<b>70 - 79</b>	37,222	3.1%	16,210	20,908
<b>80+</b>	5,006	0.4%	2,050	2,959
<b>Unknown Age</b>	3,854	0.3%	1,682	1,203

Verispan, Vector One®: Total Patient Tracker. Years 2002 - 2007. Extracted March 2008. File: TPT 2007-2425  
Bupropion AgeGender Y02-07 3-8-08.xls, TPT 2007-2425 Bupropion AgeGender Aggregate 02-07 3-8-08.xls



Verispan, Vector One®: Total Patient Tracker. Years 2002 - 2007. Extracted March 2008. File: TPT 2007-2425  
Bupropion AgeGender Aggregate 02-07 3-8-08.xls

**Table 7. VOCON Concurrency Scenario Report: Total number of patients on concurrent therapy with varenicline and products in the Antidepressant/Antipsychotic/Anxiolytic class, Year 2007**

Concurrent USC	% Concurrency	Concurrent Patients	Patients (Base - varenicline)	Patients (Conc)	Avg Concurrent Days
64110 Phenothiazine Derivatives	0%	4,775	1,470,690	137,914	5
64190 Antipsychotics Other	5%	71,076	1,470,690	2,223,519	5
64310 TCA's	5%	70,308	1,470,690	2,457,630	5
64320 MAO Inhibitors	0%	459	1,470,690	13,412	5
64330 New Gen AD's	9%	135,960	1,470,690	3,502,371	5
64340 SSRI's	19%	283,287	1,470,690	9,285,301	5
64350 SNRI's	7%	106,159	1,470,690	2,469,530	5
64380 Combination Antidepressants	0%	2,154	1,470,690	59,697	5
64610 Benzo's	16%	230,227	1,470,690	7,818,876	4
64690 Antianxiety Other	3%	43,017	1,470,690	2,189,261	4
64900 Miscellaneous	0%	2,676	1,470,690	49,962	4
<b>Overall Concurrency:</b>	<b>39%</b>	<b>569,782</b>	<b>1,470,690</b>	<b>20,286,221</b>	<b>5</b>

Verispan, Vector One: Concurrency. Year 2007. Extracted 6-10-08. Files: VOCON 2007-2425 Chantix Y2007 6-9-08.xls, Chantix Y2007 Concurrent USC 6-10-08.xls

**Table 8. VOCON Concurrency Scenario Report: Total number of patients on concurrent therapy with Buproban/Zyban and products in the Antidepressant/Antipsychotic/Anxiolytic class, Year 2007**

Concurrent USC	% Concurrency	Concurrent Patients	Patients (Base - Buproban/Zyban)	Patients (Conc)	Avg Concurrent Days
64110 Phenothiazine Derivatives	0%	36	8,141	114,736	60
64190 Antipsychotics Other	5%	441	8,141	1,890,859	58
64310 TCA's	5%	422	8,141	1,969,238	61
64330 New Gen AD's	17%	1,403	8,141	2,789,614	35
64340 SSRI's	16%	1,300	8,141	7,887,444	57
64350 SNRI's	5%	421	8,141	2,061,245	58
64380 Combination Antidepressants	0%	8	8,141	50,006	50
64610 Benzo's	14%	1,101	8,141	6,229,933	46
64690 Antianxiety Other	3%	265	8,141	1,536,707	43
<b>Overall Concurrency</b>	<b>39%</b>	<b>3,205</b>	<b>8,141</b>	<b>17,076,864</b>	<b>53</b>

Verispan, Vector One: Concurrency. Year 2007. Extracted 6-10-08. Files: VOCON 2007-2425 BupZyb Y2007 6-9-08.xls, BupZyb Y2007 Concurrent USC 6-10-08.xls

## APPENDIX 6: DATABASE DESCRIPTIONS

### ***IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail***

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### ***Verispan, LLC: Vector One®: National (VONA)***

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

### ***Verispan, LLC: Vector One®: Total Patient Tracker (TPT)***

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

### ***Verispan, LLC: Vector One®: Verispan Concurrency (VOCON)***

Data used in VOCON is derived from Verispan's Vector One® database. The Vector One® database integrates prescription activity from a variety of sources, including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims annually, representing over 160 million unique patients. Vector One® receives approximately half of retail prescriptions dispensed nationwide. Verispan obtains all prescriptions from approximately



one-third of the reporting stores and a significant sample of prescriptions from the remaining stores.

VOCON allows users to measure and evaluate concurrent drug therapy usage in unique patients during a selected time period using four scenarios. These scenarios are (in order of most to least restrictive): Same day fills, overlapping days supply, overlapping days supply with % grace period, fills during the same time period.

The VOCON module provides unprojected patients counts. Nationwide projections are not available.

### ***Verispan, LLC: Physician Drug & Diagnosis Audit (PDDA)***

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

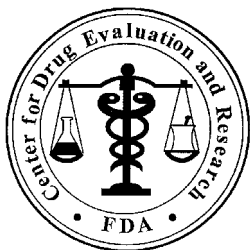
Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

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/s/

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Martin Pollock  
7/16/2008 11:09:13 AM  
DRUG SAFETY OFFICE REVIEWER

Ann W McMahon  
7/16/2008 11:30:34 AM  
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date:	12/8/08
To:	Bob Rappaport M.D., Director Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Through:	Ann McMahon, M.D., M.S., Acting Director Yoo Jung Chang, Pharm. D., Acting Team Leader Division of Pharmacovigilance II (DPV-II)  Solomon Iyasu, M.D., Director Rita-Ouellet-Hellstrom, Ph.D., Acting Team Leader Division of Epidemiology (DEPI)
From:	Martin Pollock, Pharm. D., Safety Evaluator Division of Pharmacovigilance II  Andrew Mosholder, M.D., Epidemiologist Julia Ju, PharmD, Ph.D., Pharmacoepidemiologist Division of Epidemiology
Subject:	Psychiatric events (excluding suicides)
Drug Name(s):	Varenicline and bupropion
Application Type/Number:	021928 (varenicline; Chantix); 020711 (bupropion; Zyban) <sup>1</sup> ;
Applicant/sponsor:	Pfizer (varenicline); GSK (bupropion; Zyban)
OSE RCM #:	2008-1291

**\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\***

<sup>1</sup>Also available as generic (Buproban, Teva Pharmaceuticals).

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## EXECUTIVE SUMMARY

Varenicline (Chantix; Pfizer; NDA 21928) is a smoking cessation drug approved on 5/10/06. This consult reviews AERS reports of *non-suicidal* psychiatric events (psychosis/mania, aggression/violent behavior, and miscellaneous) associated with varenicline and bupropion. This is the *second* review in response to a request from the Division of Analgesics, Anesthetics, and Rheumatology Drug Products (DAARP); the first OSE consult reviewed the AERS reports of suicidality associated with varenicline, bupropion, and transdermal nicotine.<sup>2</sup> Bupropion and nicotine replacement therapy are the only two approved alternatives to varenicline. Due to the limited findings (small number of usable cases) for transdermal nicotine in the suicidality review, only bupropion was used as the comparator in this review.

### AERS CASES

The AERS case series for non-suicidal psychiatric events for the early (417 days) of varenicline marketing (pre-stimulated reporting) and a comparable period for bupropion consisted of 625 US reports. The case series was mostly varenicline (526/625; 84%) vs. bupropion (99/625; 16%).

For both drugs, most (~80%) of the cases reported miscellaneous events.<sup>3</sup> Anxiety and depression were the two most commonly reported events for both drugs. For both drugs, ~20% of the cases reported psychosis/mania or aggression-events. For varenicline, the most common event for the psychosis/mania and aggression groups was *hallucination* and *aggression* respectively; for bupropion it was *paranoia* and *hostility* respectively.

There was a temporal association between the two drugs and all groups of events with a median onset time between 3 and 7 days. Positive dechallenge was reported in 33% and 63% of the varenicline and bupropion cases respectively.

For all event groups, patients with no reported psychiatric history ranged from 17 to 33% for varenicline and 13 to 30% for bupropion.

More varenicline patients (27%-53%) had a history of psychiatric disease than bupropion (0%-20%); however, there was a portion of the bupropion population for which unknown medical history was very high (78%). The most commonly reported psychiatric history across the case series was depression and bipolar disorder.

For all event groups, patients with no reported concomitant psychiatric medications ranged from 4 % to 13% for varenicline and 0 to 25% for bupropion. Psychiatric medication use ranged from 13 to 73% for varenicline and 21% to 70% for bupropion. The most commonly reported drug classes for varenicline and bupropion was antidepressants for psychosis/mania and aggression and benzodiazepines for the miscellaneous groups.

There were more cases of varenicline (29-33%) that reported a behavioral change from the patient's past (i.e., either new experience of disease worsening) than with bupropion (0-9%).

Although only a minority of patients (varenicline 7%; bupropion 8%) reported smoking at the time of their event(s) this can be considered evidence that the psychiatric event(s) can occur independently of nicotine withdrawal.

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<sup>2</sup>The first review was completed on 7/16/08: Pollock M, Lee J, Mosholder M, Governele L. OSE postmarketing review: Suicidality with smoking cessation drugs (varenicline, bupropion, nicotine transdermal patch); OSE RCM# 2007-2425.

<sup>3</sup>Because the reports with miscellaneous events were such a large proportion of the population, only a sample was hands on reviewed. All of the reports with psychosis/mania and aggression-events were hands on reviewed.

There were a few varenicline patients (psychosis mania, n=3; aggression, n=1) that had concomitant alcohol use and appeared to experience an interaction between varenicline and alcohol. The limited mention (varenicline 8%; bupropion 9%) of alcohol status for both drugs did not allow assessment of the effect of alcohol on the psychiatric events. Additional information about the effects of alcohol may come from a thorough review of the sponsor's postmarketing adverse event database and or from new clinical trials where alcohol-related medical history is not excluded and alcohol consumption is recorded.

## EPIDEMIOLOGY

A review of the literature disclosed some evidence from observational studies that smoking cessation is associated with new or exacerbated depression. Domestic reporting rates for spontaneous reports of aggression or psychosis were higher for varenicline than for Zyban, in the time period predating widespread publicity regarding varenicline and adverse psychiatric events. Disproportionality of reporting, as measured by the WebVDME data mining tool, showed disproportionate reporting of psychotic and aggressive events with varenicline, and to a lesser degree with Zyban. Clinical trial data analyzed by Pfizer showed somewhat higher rates of events designated "Disturbances in thinking and perception" relative to placebo, but importantly did not include data on patients with psychiatric disorders, who were generally excluded from the trials. However, a smoking cessation study in Post Traumatic Stress Disorder patients being conducted by the Department of Veterans' Affairs, study CSP-519, may provide some systematic data on adverse psychiatric events with varenicline. "Significant psychiatric adverse effects" reportedly have occurred in 7.9% of the patients treated with varenicline (19/241) and in 4.0% of the patients who did not receive varenicline (28/704). However, varenicline treatment was not randomly assigned in this trial. OSE plans to try to contact the VA study team directly to try and learn more.

## RECOMMENDATIONS

**Epidemiology:** Efforts should continue to be made to obtain more data from the VA study CSP-519.

### Varenicline labeling:

OSE recommends adding additional information concerning non-suicidal psychiatric events identified in this review in the **Adverse Reactions and Warning Sections** to both the varenicline and Zyban labels. In the case of varenicline, OSE recommends expanded information in the Boxed Warning that OSE has already proposed in its suicidality review.<sup>2</sup> A complete presentation of the varenicline labeling recommendations for non-suicidal psychiatric events is in **Section 6**.

Specific additions to the **varenicline** labeling are as follows:

#### Box Warning

Patients taking Chantix should be observed for the following events: *anger, delusion, homicidal ideation, mania, paranoia, and psychosis*.

Pre-existing psychiatric illness and symptoms and can be worsened after taking Chantix:

*anger, anxiety, bipolar disorder, depression, hallucinations, mania, panic disorders psychosis, and schizophrenia.*

#### ADVERSE REACTIONS/Postmarketing Experience

There have been reports of *aggression, anger, delusion, homicidal ideation, mania, paranoia and psychosis*

Specific additions to **Zyban** labeling are as follows:

## **BOX WARNING AND PRECAUTIONS**

**Depression and Nicotine Withdrawal:** For suicidal ideation, delete ‘rarely’. *Enhanced nicotine withdrawal symptoms of anxiety, aggression, and emotional disorder have been reported in patients taking Zyban for smoking cessation.*

## **ADVERSE REACTIONS**

**Nervous System:** Also observed *were anger, disorientation, emotional disorder, feeling abnormal, mood altered, mood swings, psychotic disorder*

# **1 BACKGROUND**

## **1.1 INTRODUCTION**

Varenicline (Chantix; Pfizer; NDA 21928) is a smoking cessation drug approved on 5/10/06. This consult contains an AERS review of *non-suicidal* psychiatric events (psychosis/mania, aggression/violent behavior, and miscellaneous) associated with varenicline and bupropion. This is the *second* review in response to a request from the Division of Analgesics, Anesthetics, and Rheumatology Drug Products (DAARP); the first OSE consult reviewed the AERS reports of suicidality associated with varenicline, bupropion, and transdermal nicotine.<sup>4</sup> Bupropion and nicotine replacement therapy are the only two approved alternatives to varenicline. Due to the limited findings (small number of usable cases) for the transdermal nicotine in the suicidality review, only bupropion was used as the comparator in this review. This consult also contains an Epidemiology section which addresses non-suicidal psychiatric events and varenicline from (1) Pfizer’s submission of post-marketing submission, (2) published case reports, (3) AERS reporting rates, and (4) disproportionality (datamining) analysis; there is also (5) an evaluation of the literature for non-suicidal psychiatric events associated with smoking cessation.

### Regulatory history

Varenicline was approved on 5/10/06<sup>5</sup> (NDA 21928; Pfizer) in the U.S. and is indicated as an aid to smoking cessation treatment.<sup>6</sup> Varenicline (Champix) was approved in Europe on 9/26/06. In May 2007, the EMEA informed FDA that they were investigating a signal of suicidal-related events with varenicline and had asked Pfizer to submit a postmarketing suicidal-event analysis. An AERS database search on 6/26/07 retrieved 26 non-fatal suicidal-related reports.<sup>7,8</sup>

On 9/3/07, a celebrity rock-musician Carter Albrecht, who was taking varenicline for smoking cessation for one week, was shot to death by a neighbor after he exhibited violent-bizarre behavior toward his girlfriend. Albrecht’s girlfriend was widely quoted in the press saying that

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<sup>4</sup>The first review was completed on 7/16/08: Pollock M, Lee J, Mosholder M, Governele L. OSE postmarketing review: Suicidality with smoking cessation drugs (varenicline, bupropion, nicotine transdermal patch); OSE RCM# 2007-2425.

<sup>5</sup>Chantix was first distributed to U.S. wholesalers the week of 7/10/06 (personal communication with Pfizer Drug Information Department, 7/13/07).

<sup>6</sup>Chantix product labeling; INDICATIONS AND USAGE; Pfizer Labs, N.Y., N.Y. January 2008.

<sup>7</sup>Pollock M.; Varenicline and suicidality; Analysis of AERS reports for EMEA. Presented at video-con on 7/17/07. AIMS# 2007-1441.

<sup>8</sup>Chantix U.S. labeling, as initially approved listed *suicidal ideation*. The European labeling, on initial approval did not list any suicidal-related events. Champix Product Information; (<http://www.emea.europa.eu/humandocs/PDFs/EPAR/champix/H-699-PI-en.pdf>)

she believed Albrecht's unusual behavioral change was due to varenicline. While the final disposition of this case is not known, alcohol was reported to be a confounding factor.<sup>9</sup> Subsequently, additional anecdotal reports of varenicline and psychiatric-related events such as depression and suicidality started to appear in the media.<sup>10</sup> This was the start of a period of 'stimulated reporting.'

In September 2007, DAARP submitted a request to Pfizer for an analysis of postmarketing reports of suicidality and aggressive and irrational behavior associated with varenicline. In October 2007, the FDA received two submissions from Pfizer, one for suicidality (n=102; See **3.2 EPIDEMIOLOGY**) and one for aggression/hallucinations/irrational behavior (n=525). After an initial review of this data, it was decided that there appeared to be a signal for behavioral changes with varenicline and that the public should be informed. An Early Communication was issued in November 2007.<sup>11</sup> At the same time, the **ADVERSE REACTIONS** section of the varenicline labeling was revised to include reports of changes in behavior including suicidal events.

The EMEA issued a press release in December 2007 regarding the occurrence of depression and suicidality (ideation and attempt).<sup>12</sup> In February 2008, the FDA issued a Public Health Advisory.<sup>13</sup> This was accompanied by a second varenicline labeling change under **WARNINGS (See 1.3 Product Labeling)** which described neuropsychiatric symptoms. It also mentioned that the events occurred in patients who were smoking or who had quit; some patients experienced worsening of their pre-existing psychiatric history.

On 4/14/08, a Regulatory Briefing with the Center Director concerning varenicline and psychiatric-related events was held. The benefits of varenicline to help patients achieve cessation from smoking vs. the risks of psychiatric adverse events were discussed.

On 5/16/08, DAARP informed Pfizer to submit a proposed Risk Evaluation and Mitigation Strategy (REMS) for neuropsychiatric events.<sup>14</sup> The components of the REMS requested by FDA are a medication guide (approved on 5/16/08), communication plan to healthcare providers, and postmarketing clinical studies 'to assess the known serious risk of neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions.'<sup>14</sup>

The purpose of this review is to examine non-suicidal psychiatric events that have been reported with varenicline and bupropion and to provide recommendations for the management of this safety issue. The source of the data were AERS reports (performed by DPV-II) and the following other sources (performed by DEPI): (1) Pfizer's submission of post-marketing non-suicidal psychiatric events (2) published case reports, (3) AERS reporting rates, and (4) disproportionality

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<sup>9</sup>Eiserer,T Autopsy: Carter Albrecht intoxicated 3 times the legal limit. *The Dallas Morning News* 10/22/07  
./http://www.dallasnews.com/sharedcontent/dws/news/localnews/stories/102207dnmetalbrecht.197ab4f40.html

<sup>10</sup>PeoplesPharmacy.com; Can Chantix cause depression? 9/17/07; Scary side effects of Chantix 10/17/07; Stop-smoking drug linked to suicidal thoughts 12/10/07.

<sup>11</sup>Early Communication About an Ongoing Safety Review: Varenicline (marketed as Chantix); 11/20/07;  
http://www.fda.gov/cder/drug/early\_comm/varenicline.htm

<sup>12</sup>Press Release: European Medicines Agency concludes new advice to doctors land patients for Champix needed. 12/14/076. <http://www.emea.europa.eu/humandocs/PDFs/EPAR/champix/59551607en.pdf>. There was also a labeling change made.

<sup>13</sup>FDA Public Health Advisory: Important Information on Chantix (varenicline) 2/1/08;  
http://www.fda.gov/cder/drug/infopage/varenicline/default.htm

<sup>14</sup>Rappaport B (DAARP) NDA supplement (21-928/S-008) approval letter sent to 5/16/08 to Pfizer Inc. The actual details of the clinical trials are still to be determined by DAARP



(datamining) analysis; there is also (5) an evaluation of the literature for non-suicidal psychiatric events associated with smoking cessation.

## 1.2 PHARMACOLOGY

### Varenicline

Varenicline is a partial agonist<sup>15</sup> for the neuronal nicotinic acetylcholine receptor subtype  $\alpha_4\beta_2$  which is known to be involved with nicotine addiction. Varenicline-stimulation of the  $\alpha_4\beta_2$  receptor maintains dopamine levels in the brain which can prevent nicotine craving and withdrawal symptoms in the patient who is trying to quit smoking. Varenicline also makes smoking undesirable because by occupying the  $\alpha_4\beta_2$  receptor, varenicline also acts as an *antagonist* which can prevent nicotine from achieving any receptor activation.<sup>15</sup>

### Bupropion (Zyban; Buproban [generic])

The anti-smoking effect of bupropion might be accomplished through its weak inhibition of dopamine and norepinephrine reuptake as well as antagonism of the nicotinic acetylcholine receptor.<sup>16</sup> The exact mechanism of action in smoking cessation is believed to be complex and not known.<sup>16,17</sup>

## 2 METHODS

### 2.1 AERS SELECTION OF CASES

#### 2.1.1 Varenicline

The psychiatric events (excluding suicide) were categorized into three groups: 1) psychosis/mania, 2) aggression and violent behavior, and 3) miscellaneous (Table 2.1.1.1) These three categories and their respective specific MedDRA terms were the same as that used in a previous OSE review for psychiatric events associated with drugs indicated to treat Attention Deficit Hyperactivity Disorder.<sup>18</sup>

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<sup>15</sup>A partial agonist is an agonist that has a smaller maximal effect at full receptor occupancy than does the full agonist (i.e. nicotine). Varenicline has about 43% receptor efficacy compared with nicotine. Rollema J, Coe JM, Chambers LK, Hurst SR et al. Rationale, pharmacology and clinical efficacy of partial agonists of  $\alpha_4\beta_2$  nACH receptors for smoking cessation. *Trends Pharmacol. Sci.* 2007;28:316-325.

<sup>16</sup>Foley KF, DeSanty KP, Kast RE. Bupropion: pharmacology and therapeutic applications. *Future Drugs Ltd* 2006;6:1249-1265.

<sup>17</sup>Zyban labeling; Clinical Pharmacology; GlaxoSmithKline, Research Triangle Park, N.C.; September, 2006.

<sup>18</sup>Galperin K, Phelan K. *Psychiatric events associated with drugs to treat ADHD*: Review of postmarketing safety data. Division of Drug Risk Evaluation; Office of Drug Safety; D050243; March 3, 2006.

**Table 2.1.1.1 MedDRA Preferred terms (PTs) for the three selected categories of psychiatric events<sup>18</sup>**

<b>Psychosis/mania</b>	<b>Aggression and violent behavior</b>	<b>Miscellaneous</b>
Mania	Aggression	Abnormal behaviour
Paranoia	Belligerence	Amnesic symptoms (HLT)
Catatonia	Anger	Confusional state
Hypomania	Hostility	Mood alterations with depressive symptoms (HLT)
Schizotypal personality disorder	Physical assault	Depression
Schizophrenia and other psychotic disorders (HLGT)	Sexual abuse <sup>19</sup>	Major depression
Delusional symptoms (HLT)	Murder	Disorientation
Perception disturbances (HLT)	Imprisonment	Emotional disorder
Bipolar disorders (HLT)	Homicidal ideation	Emotional distress
Schizoid personality disorder		Feeling abnormal
Paranoid personality disorder		Mood altered
		Mood swings
		Personality change
		Thinking abnormal
		Anxiety disorders with symptoms (HLGT)
		Trichotillomania <sup>20</sup>
		Sleep disorder
		Tic disorders (HLT)

<sup>19</sup>*Sexual offence*; was the MedDRA term in the original criteria; now changed to sexual abuse.

<sup>20</sup>*Hair plucking* was the MedDRA term in the original criteria; now changed to Trichotillomania.

In order to avoid the period of ‘stimulated reporting’ which started in September, 2007 (see Section 1.2 above), reports received on or before 8/31/07 was chosen as the cut-off date for this review. As varenicline was first distributed to U.S. wholesalers the week of 7/10/06, the time period ending on 8/31/07 represents the first 417 days of the product marketing.

On 6/10/07 the AERS database was searched for the suspect drug, varenicline, for U.S. reports<sup>21</sup> from 7/10/06 until 8/31/07 for reports of psychosis/mania, aggression, and other miscellaneous events as listed in Table 2.1.1.1

For all cases, particular attention was focused on identifying those reports where it was stated that the behavior change associated with the particular event(s) was a significant change from the past, i.e. prior to taking varenicline:

- (1) The suicidal event(s) were a first-time occurrence for the patient, i.e. the patient had no history or remembrance of ever having experienced such an event(s) or
- (2) The patient had a history of a psychiatric disease, but was being adequately treated and or was felt to be under control. After taking varenicline, the pre-existing psychiatric disease worsened.

### 2.1.2 Bupropion

The time period for the AERS search of bupropion reports was made comparable to varenicline such that the first 417 days of Zyban marketing was captured. Zyban was first marketed on 5/15/97, and therefore, the comparable 417 day marketing period ended on 7/15/98.

On 6/10/07, the AERS database was searched for the suspect drug, bupropion, for all U.S.<sup>21</sup> reports from 5/15/97 to 7/15/98. The reports were then extracted from AERS and further processed in Microsoft Office<sup>®</sup> Access.<sup>22</sup> Reports were retrieved that met the following criteria:

- (1) trade name of Zyban or indication of smoking cessation  
and
- (2) one or more of the MedDRA terms for each psychiatric event group listed in Table 2.1.1.1.

As noted above, particular attention was focused on reports that were identified with significant behavioral changes from the past, as explained for varenicline in 2.1.1 (above).

Although Zyban is marketed exclusively for smoking cessation, a patient could also be taking a generic or Wellbutrin for his/her antismoking therapy. Therefore, this broad search strategy, using drug name and indication was adopted to capture as many reports as possible.

### 2.1.3 Concomitant Medications

Concomitant medication were evaluated as two classes: psychiatric and non-psychiatric medications. *Psychiatric medications* were those drugs what are approved to treat psychiatric conditions listed in DSM-IV<sup>23</sup> such as anxiety, mood, psychotic, schizophrenic, dissociative,

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<sup>21</sup>Reports were also captured for NULL country. From previous experience with varenicline, it has been found that most of the NULL country reports were from the U.S. Any foreign cases were eliminated in the individual case review.

<sup>22</sup>The extract is a file that contains 206 different fields from the MedWatch (or electronically submitted) report. The relevant fields examined included all suspect drugs, drug name (verbatim and trade), total dose, indication, all reactions and narrative.

<sup>23</sup>Diagnostic and statistical manual of mental disorders 4<sup>th</sup> ed. text revision (2000). American Psychiatric Association, Arlington, VA;

sleep, eating and personality disorders. Such medications were classified as ‘psychiatric’ whether the indication was stated in the report or not. *Non-psychiatric medications* that are labeled for the particular event(s) were also evaluated.

#### **2.1.4 Randomized Sampling**

The desired number of total reports to be reviewed for both drugs and all three events categories was set at about 300. Using the criteria mentioned in 2.1.1 and 2.1.2 the crude counts for all three event categories (varenicline 618; bupropion 135) showed that the majority of reports for both drugs were the miscellaneous psychiatric event group (varenicline 461[75%]; bupropion 115 [85%]). The combined crude counts for the psychosis/mania and the aggression groups for both drugs was 177 and this number was manageable such that all reports were reviewed. This left about 123 (300 minus 177; to be split between the two drugs to be selected for the miscellaneous psychiatric event group. To keep the total number of reports to a manageable number for the manual review of the miscellaneous psychiatric event group, a 10% random sample (n=47) of the 461 varenicline reports and a 50% random sample (n=58) of the 115 bupropion reports were selected. To select the two samples, random numbers generated using Microsoft Excel’s random number generator RAND() were used. For both drugs and all three event categories, the total number of reports for hands-on-review was 282.

## **2.2 EPIDEMIOLOGY**

### **2.2.1. Sponsor’s information**

The following sources of information from the sponsor were reviewed: (1) the sponsor’s analysis of aggressive and irrational behavioral events in varenicline clinical trials, submitted 10-23-07; (2) the sponsor’s analysis of postmarketing reports of aggressive or irrational behavioral events with varenicline treatment, submitted on the same date.

### **2.2.2 Case Reports and Literature Review**

A literature review was conducted in MEDLINE to identify published studies and case reports/series that evaluate the association between smoking cessation and psychiatric events. Various permutations of MeSH terms (e.g. “Psychotic Disorders”; “Mood Disorders”; “Depression”; “Depressive Disorders”; “Smoking Cessation”; and keywords (“smoking cessation”; “nicotine withdrawal”; “mania”; “violence”; “aggression”; “aggressive behavior”; “suicide”; “hostility”; “depression”; “depressive”; “psychosis”; “psychotic”; “psychiatric”; “event”; “episode”; “exacerbation”) were used to retrieve articles of interest. The abstracts of all articles retrieved by the search were reviewed to identify articles reporting on the association of interest. When possible, the full-text versions of the articles were obtained and reviewed. When full-text versions were not available, data were extracted from the abstracts.

The objectives of this literature review include:

1. To assist in understanding if smoking cessation alone may be associated with specific neuropsychiatric events;
2. To examine whether preexisting mental illness increases the risk of developing neuropsychiatric events after smoking cessation.

### 2.2.3 Reporting rates for psychiatric events

Reporting rates for psychotic and aggressive adverse events were calculated for varenicline for the time period from NDA approval (5-10-06) through 8-31-07; the latter date was chosen because it was just prior to the publicity regarding neuropsychiatric adverse events with varenicline, which may have stimulated reporting (see discussion in previous OSE consult regarding suicidality events or section 2.1.1. in this consult). Chantix was not launched until two months after its NDA approval, while Zyban was launched as soon as it was approved. Accordingly, the time frame chosen for Zyban reports, 5-14-97 to 7-5-98, was correspondingly shorter than the period selected for Chantix. The count of adverse event reports was determined by the AERS case review of reports for each drug product; cases with an FDA receipt date falling during the relevant time period were included in the numerator. The denominator was the number of total prescriptions dispensed for the product according to Verispan, LLC: Vector One®: National (VONA) during that period of time. The denominator, intended to be the same as those used for the reporting rates in the previous review on suicide, was corrected to include both new prescriptions and refills. The previous report included only new prescriptions (see erratum in Appendix 6). We used prescriptions for Zyban as a proxy for bupropion's use in smoking cessation, although Wellbutrin brand products may also have been used for this indication. Consequently, reporting rate results for bupropion will be over-estimated.

### 2.2.4 Disproportionality Analysis

Data mining on the AERS database for reports involving Chantix or Zyban as suspect drugs was performed on data through 2007<sup>24</sup>. The WebVDME data mining application was used to assess reporting of the preferred terms in the AERS search described herein.

A data mining analysis of the Adverse Event Reporting System (AERS) database was performed for this review. This analysis used the Multi-item Gamma Poisson Shrinker (MGPS)<sup>25,26</sup> algorithm which analyzes the records contained in the large post-marketing drug safety databases, such as AERS. The algorithm then quantifies reported drug-event associations by producing a set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database being analyzed. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted EB05 and EB95 respectively.

## 3 RESULTS

### 3.1 AERS CASES

The total number of reports retrieved for both drugs during the first 417 days of marketing for the three groups of psychiatric events (excluding suicides) was 753 (crude count; varenicline 618; bupropion 135). The total number of reports actually reviewed was 282 (takes into account 10% and 50% sampling of miscellaneous group for varenicline and bupropion, respectively; see 2.1.4).

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<sup>24</sup> Data mining analysis provided by Dr. Rita Ouellet-Hellstrom

<sup>25</sup> DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76

<sup>26</sup> Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392

Appendix 2 shows selected parameters (e.g. demography, report type, reporter, FDA received date, outcome) for the full and sampled populations for varenicline (n=461; n=47) and bupropion (n=115; n=58) for the miscellaneous psychiatric events.

Tables 3.1.1 and 3.1.2 list AERS cases that were excluded (n=39) and included (n=243) for varenicline and bupropion case series, respectively.

**Table 3.1.1 Varenicline: Included/Excluded AERS cases** (numbers in parentheses for included cases represent the case count after applying the sampling ratio for miscellaneous events)

Event category	Crude counts (N)	Excluded Cases		Included cases (n)
		Reason for exclusion	n	
Psychosis/mania	109	Duplicate	1	98
		Event occurred before varenicline exposure	7	
		Event was miscoded	1	
		Could not determine if patient was taking varenicline before event occurred	1	
		Event due to other underlying condition (extensive rash) <sup>27</sup>	1	
Aggression	48	No exclusions	0	48
Miscellaneous	47 <sup>28</sup>	Event associated with other (non-psychiatric) underlying disease or condition	4	38 (380)
		Not known if patient was taking varenicline at the time of event	3	
		Event occurred before varenicline exposure	1	
		Event (personality change) had positive outcome ('patient became nicer')	1	
Total	204		20	184 (526)

**Table 3.1.2 Bupropion: Included/Excluded cases** (numbers in parentheses for included cases represent the case count after applying the sampling ratio for miscellaneous events)

Event category	Crude counts (N)	Excluded Cases		Included cases (n)
		Reason for exclusion	n	
Psychosis/mania	11	No exclusions	0	11
Aggression	9	Report coded for 'anger' but	1	8

<sup>27</sup>A female (unknown age, medical history and concomitant medications), had swelling (coded as rash and erythema) over most of her body (including face) after taking varenicline. The rash felt like 'deep needles and ants all over her body and inside her head' (coded as paresthesia and *formication*).

<sup>28</sup>Represents 10% sample; total population was 461.

Event category	Crude counts (N)	Excluded Cases		Included cases (n)
		Reason for exclusion	n	
		anger was not experienced		
Miscellaneous	58 <sup>29</sup>	Event associated with other (non-psychiatric) underlying disease or condition	18	40 (80)
Total	78		19	59 (99)

The demographics and other selected information regarding the varenicline and bupropion case series for 1) psychosis/mania, 2) aggression, and 3) miscellaneous psychiatric events are provided in Tables 3.1.3, 3.1.4, and 3.1.5, respectively.

**Table 3.1.3 Demographics and other selected information for AERS cases of psychosis/mania** (data are not necessarily mutually exclusive)

Parameter	Varenicline (n=98)	Bupropion (n=11)
Age (years)	n=82 mean 47.9; median 48; range 23-73	n=8 mean 57.5; median 60; range 40-75
Sex	n=94	
Male	30	3
Female	64	8
Event onset while taking smoking cessation drug	Yes 94; no 4	Yes 11
Event onset (days) while taking smoking cessation drug	n=49; mean 10.6 median 6; range 1-70	n=5; mean 5.5; median 3.5 range 1-16
Event onset (days) after smoking cessation drug discontinued	n=2 (3,21)	0
Smoking cessation drug discontinued	Yes 54; no 20; unknown 24	Yes 7; no 2; unknown 2

<sup>29</sup>Represents 50% sample; total population was 115.

Parameter	Varenicline (n=98)	Bupropion (n=11)	
<b>Dose (at time of event)</b>	n=45	n=5	
Within recommended	42	3	
Lower than recommended	3	0	
Higher than recommended	0	1	
Not able to be determined	0	1	
<b>Reported event(s)</b>			
Hallucination	41	1	
No further descriptor	22		
auditory	8	1	
visual	6		
tactile	3		
mixed	1		
olfactory	1		
Paranoia	20	5	
Manic-related	20	1	
mania	18	1	
hypomania	2		
Bipolar disorder	16 <sup>30</sup>		
Psychotic disorder	10	3	
Delusion	5		
Perception disturbance	4	2	
illusion	1		
derealisation	1	1	
delusional perception	1		
flashback	1	1	
Schizophrenia	3		
Formication	3		
<b>Other co-reported psychiatric-related events (Top 5)<sup>31</sup></b>			
Varenicline (n=74)		Bupropion (n=9)	
Abnormal dreams	17	Insomnia	4
Insomnia	15	Disorientation	3
Anxiety	13	Anxiety	3
Feeling abnormal	12	Nervousness	2
Irritability	8	Other events <sup>32</sup>	1

<sup>30</sup>In ten of these cases, the patient had pre-existing bipolar disorder and it worsened after varenicline exposure.

<sup>31</sup>Full listing of reported events for varenicline is given in Appendix 3.

<sup>32</sup>There were 11 events (each reported once): agitation, crying, depression, emotional disorder, emotional distress, hostility, memory impairment, panic attack, post-traumatic stress disorder, psychomotor hyperactivity, tremor



Parameter	Varenicline (n=98)	Bupropion (n=11)
<b>Psychiatric-related history</b>	n=69	n=5
No	17	3
Yes	52	2
Bipolar	22	2
Depression	15	
Schizophrenia	9	1
Anxiety	5	
Post traumatic stress disorder	3	
Psychiatric hospitalization	3	
Mania	2	
Attention deficit disorder	2	
Panic attacks	2	
Hallucination	2	
Anorexia	1	
Confusion <sup>33</sup>	1	
Emotional disorder	1	
Abnormal dreams	1	
Mental health problems NOS	1	
Multiple personality disorder	1	
Paranoid schizoaffective	1	
Sleep talking	1	
Thinking abnormal	1	
Menopausal <sup>34</sup>	1	
Traumatic brain injury <sup>35</sup>	1	
<b>Concomitant medication</b>		
Unknown	22 <sup>38</sup>	8 <sup>40</sup>
No	4	0
Yes	72	3
Psychiatric-related	58	3
Antidepressant	43	2
Antipsychotic	28	2
Mood stabilizer/AED <sup>36</sup>	26	2
Benzodiazepine	17	
Antianxiety	15	1
Sedative	10	1
Stimulant	4	
Anti-panic attack <sup>37</sup>	1	
Other psych med(s) NOS	4	
Other med(s) labeled for psychiatric event	25 <sup>39</sup>	0

<sup>33</sup>Also has history of depression.

<sup>34</sup>A 49-year-old female experienced delusion and paranoia after discontinuing varenicline. In addition to suspecting varenicline, “she was also menopausal and suggested this might be a reason for the symptoms she was experiencing.”

<sup>35</sup>A 44-year-old female experienced formication after taking Chantix. About 3 years before she took Chantix, she sustained a brain injury due to oxygen deprivation. The report stated that “she is taking Adderall (amphetamine) for the brain injury.” Adderall is indicated for Attention Deficit Hyperactivity Disorder (ADHD) and Narcolepsy.

<sup>36</sup>AED=antiepileptic drug.

<sup>37</sup>Propranolol.

Parameter	Varenicline (n=98)	Bupropion (n=11)
<b>Smoking information</b>		
Smoking status at time of event	n=22	n=0
Quit	11	0
Smoking	11	0
Smoking duration (years)	n=2 (37,40)	n=2 (20, 46)
Number of packs per day	n=10; average 1.7; median 1.5 range 1-3	n=0
Prior cessation attempt	n=3; nicotine gum&patch (n=1); nicotine gum (n=1); unk (n=1)	n=0
Enrolled in Get Quit (Pfizer support program)	8	Not applicable
<b>Significant change in behavior from past</b>		
New psychiatric experience	n=28 8	n=1 1
Psychiatric disease worsening	20	0
Bipolar	12	
Hallucination	4	
Mania	2	
Psychosis	1	
Schizophrenia	1	
<b>Substance use/abuse including alcohol</b>		
Alcohol	n=16 15	n=1 1
No use at any time	5	
No history of abuse	1	
History of use	3	
History of abuse	3	1
Concomitant use	3	
Methamphetamine history of abuse	1	
Marijuana and cocaine concurrent use	1	
<b>Outcome</b>		
Serious	96 94	4
Hospitalization	14	1
Life-threatening	2	
Disability	2	1
Other	93 <sup>41</sup>	4
Non-serious	2	7
<b>Recovery</b>		
Yes	59 39	8 7

<sup>38</sup>In four reports, for at least one of the concomitant non-psychiatric medications, the specific product name (generic or trade) was not given. If there were other listed medications, the medications were not psychiatric related and not labeled for the psychosis/mania-related event(s).

<sup>39</sup>The patients taking 1) medication(s) that were psychiatric-related and 2) other medication(s) labeled for the event are not mutually exclusive. For varenicline, the number of patients that were taking both of these groups of medications was 62.

<sup>40</sup>In one report, for at least one of the concomitant non-psychiatric medications, the specific product name (generic or trade) was not given. If there were other listed medications, the medications were not psychiatric related and not labeled for the psychosis/mania-related event(s).

<sup>41</sup>Three of the patients had emergency room visits.

Parameter	Varenicline (n=98)	Bupropion (n=11)
Partial	5	
No	15	1
<b>Dechallenge</b>	n=44	n=9
Positive	37	8
Negative	7	1
<b>Rechallenge, positive</b>	2	0
<b>FDA received year</b>		
1997		6
1998		5
2006	12	
2007	86	
<b>Report type</b>		
Expedited	91	1
Periodic	1	10
Direct	6	
<b>Reporter</b>		
Healthcare professional	63	6
Published literature	2 <sup>42,43</sup>	0
Consumer	35	5
Solicited by sponsor	12	0

**Table 3.1.4 Demographics and other selected information for AERS cases of aggression**  
(data are not necessarily mutually exclusive)

Parameter	Varenicline (n=48) <sup>44</sup>	Bupropion (n=8)
<b>Age (years)</b>	n=38 mean 46.5; median 47.5; range 26-62	mean 49.5; median 53.5; range 32-60
<b>Sex</b>	n=47	
Male	12	1
Female	35	7
Event onset while taking smoking cessation drug	Yes 46; No 1; unknown 1	Yes 8
Event onset (days) while taking smoking cessation drug	n=24; mean 10.2; median 7; range 3-28	n=4; mean 7.5 ;median 7; range 2-14
Event onset (days) after smoking cessation drug discontinued	n=1 (1)	n=0
Smoking cessation drug discontinued	Yes 24; no 13; unknown 11	Yes 7; no 1
<b>Dose (at time of event)</b>	n=21	n=4
Within recommended	19	3
Lower than recommended	1	
Higher than recommended	1 <sup>45</sup>	1

<sup>42</sup>Freedman R. Exacerbation of schizophrenia by varenicline. *Am. J. Psychiatry* 2007;164:1269.

<sup>43</sup>Kohen I, Kreman N. Varenicline-induced manic episode in a patient with bipolar disorder. *Am. J. Psychiatry* 2007;64:1269-1270.

<sup>44</sup>For the different parameters, if the total number of cases that were evaluable is not specified, this means it was the same as the number of cases that were included in the particular drug/event group, i.e. varenicline (n=48) and bupropion (n=8).

<sup>45</sup>One patient (53-year-old female; ISR# 5400804) took varenicline for 7 months. During the second month of therapy she was hospitalized due to an overdose with varenicline (actual dose unknown). A varenicline dose of 2 mg/day was

Parameter		Varenicline (n=48) <sup>44</sup>	Bupropion (n=8)
<b>Reported event(s)</b>			
Aggression		20	2
Anger		19	3
Homicidal ideation		18	0
Hostility		1	5
<b>Other co-reported psychiatric-related events (Top 5)<sup>46</sup></b>			
Varenicline (n=43)		Bupropion (n=8)	
Insomnia	8	Depression	3
Anxiety	8	Insomnia	3
Abnormal dreams	7	Mood swings	2
Depression	7	Irritability	2
Irritability	7	Other <sup>47</sup>	1
<b>Psychiatric-related history</b>		n=28	n=1
No		16	1
Yes		12	0
Depression		5	
Bipolar		5	
Suicidality <sup>48</sup>		2	
Schizophrenia		2	
Psychiatric hospitalization		1	
Mood changes		1	
Hyperactivity		1	
Anxiety		1	
Anger		1	
<b>Concomitant medication</b>			
Unknown		11 <sup>50</sup>	2
No		6	2
Yes		31	4
Psychiatric-related		24	2
Antidepressant		18	1
Benzodiazepine		9	1
Antipsychotic		9	
Mood stabilizer/AED <sup>49</sup>		5	
Sedative		4	
Stimulant		1	
Other med(s) labeled for psychiatric event		6	0

also mentioned as the ‘normal dose’ the patient took over the 7 months. At an unknown time the patient became *combative* (temporal relationship to varenicline exposure, either 2 mg/day or ‘overdose’ was unknown).

<sup>46</sup>Full listing of reported events for varenicline is given in Appendix 4.

<sup>47</sup>There were 11 events (each reported once): tobacco withdrawal symptoms, suicidal ideation, nervousness, emotional distress, emotional disorder, disturbance in attention, dissociation, disorientation, crying, and agitation.

<sup>48</sup>One case reported suicidal ideation. A second case reported suicidal behavior: at an unknown time before taking varenicline, the patient, who also had a history of ‘being moody’ and having ‘emotional ups and downs’ and was also taking Neurontin (for neuropathic pain), became ‘suicidal.’ The details of the suicidal behavior were unknown.

<sup>49</sup>AED=antiepileptic drug

<sup>50</sup>In four reports, for at least one of the concomitant non-psychiatric medications, the specific product name (generic or trade) was not given. If there were other listed medications, the medications were not psychiatric related and not labeled for the aggression-related event(s).

Parameter	Varenicline (n=48) <sup>44</sup>	Bupropion (n=8)
<b>Smoking information</b>		
Smoking status at time of event	n=15	n=1
Quit	7	1
Smoking	8	0
Smoking duration (years)	n=1 (30)	n=1 (15)
Number of packs per day (ppd)	n=4; median 1.5 ppd; range 1-2 ppd	n=0
Prior cessation attempt	n=3; bupropion 1; hypnosis 1; method/drug unknown 1	n=0
Enrolled in Get Quit (Pfizer support program)	n=4	Not applicable
<b>Significant change in behavior from past</b>	n=16	
New psychiatric experience	12	n=0
Psychiatric disease worsening	4	n=0
Anger	2	
Hyperactivity	1	
Emotional distress	1	
Psychosis	1	
Mania	1	
<b>Substance/use abuse including alcohol</b>	n=8	n=0
Alcohol	8	
No use at any time	2	
No history of abuse	1	
History of use	1	
History of abuse	4	
Concomitant use	1	
Methamphetamine history of abuse	1	
<b>Outcome</b>		
Serious	48	2
Hospitalization	1	
Life-threatening	0	1
Disability	1	
Other	48	1
Non-serious	0	6
<b>Recovery</b>	n=24	n=7
Yes	12	7
Partial	0	
No	12	
<b>Dechallenge</b>	n=15	n=7
Positive	11	7
Negative	4	0
<b>Rechallenge, positive</b>	0	0
<b>FDA received year</b>		
1997		4
1998		4
2006	6	
2007	42	
<b>Report type</b>		
Expedited	44	1
Periodic	0	6
Direct	4	1

Parameter	Varenicline (n=48) <sup>44</sup>	Bupropion (n=8)
<b>Reporter</b>		
Healthcare professional	16	3
Consumer	32 <sup>51</sup>	5

**Table 3.1.5 Demographic and other selected information for AERS cases of miscellaneous psychiatric events** (data are not necessarily mutually exclusive)

Results are presented for both the cases reviewed and the expected number after adjusting for the sampling fraction ( $n_f$ ) (refer to Section 2.1.3.2)

Parameter	Varenicline (n=38) (380)	Bupropion (n=40) (80)
<b>Age (years)</b>	n=33 (330) Mean 50.3 ; median 49; range 31-83	n=39 (78) Mean 49.6; median 46; range 30-70
<b>Sex</b>		
Male	9 (90)	16 (32)
Female	29 (290)	24 (48)
Event onset while taking smoking cessation drug	Yes 35 (350); no 3 (30)	Yes 40 (80)
Event onset while taking smoking cessation drug in days	n=23 (230); mean 8.6; median 3; range 1-42	n=22 (44); mean 9.4; median 6.5; range 1-64
Event onset after smoking cessation drug discontinued [days]	n=2 (20); [1, 4]	n=1 (2); <sup>52</sup> [2]
Smoking cessation drug discontinued	Yes 22 (220); no 10 (100); unknown 6 (60)	Yes 23 (46); no 9 (18); unknown 8 (16)
<b>Dose at time of event</b>	n=22 (220)	n=30 (60)
Within recommended	20 (200)	16 (32)
Lower than recommended	1 (10)	1 (2)
Higher than recommended	1 (10)	3 (6)
Could not be determined	0 (0)	10 <sup>53</sup> (20)

<sup>51</sup>Eleven of the reports were solicited by Pfizer. Pfizer conducts marketing and smoking support programs for Chantix where patients are contacted by telephone to ascertain the patient's progress in quitting smoking. If the patient reported any adverse events during these contacts, these reports are considered 'solicited' by OSE and Pfizer.

<sup>52</sup>The same patient experienced depression while taking bupropion for an unknown time and then 'became emotional' (coded as *emotional disorder PT*) within two days after bupropion was discontinued.

<sup>53</sup>Ten patients had a dose of 300 mg/daily, but it could not be determined if the patient was within the first 3 days or in the 4<sup>th</sup> day or beyond of bupropion therapy. The recommended dose for these time periods are 150 mg and 300 mg per day, respectively.

Parameter	Varenicline (n=38) (380)	Bupropion (n=40) (80)
<b>Reported event(s)</b> <sup>54</sup>		
Anxiety	13 (130)	12 (24)
Feeling abnormal	11 (110)	4 (8)
Depression	9 (90)	10 (20)
Panic attack	5 (50)	1 (2)
Amnesia	3 (30)	2 (4)
Emotional disorder	4 (40)	3 (6)
Agitation	3 (30)	7 (14)
Nervousness <sup>55</sup>	3 (30)	6 (12)
Mood swings	2 (20)	3 (6)
Fear	2 (20)	1 (2)
Abnormal behaviour	2 (20)	0 (0)
Confusional state	2 (20)	1 (2)
Personality change	2 (20)	0 (0)
Disorientation	2 (20)	3 (6)
Sleep disorder	2 (20)	0 (0)
Claustrophobia	1 (10)	0 (0)
Thinking abnormal	1 (1)	1 (2)
Stress <sup>56</sup>	1 (1)	0 (0)
<b>Other co-reported psychiatric-related events (Top 5)</b> <sup>57</sup>		
Varenicline (n=24) (240)	Bupropion (n=26) (52)	

<sup>54</sup>For **varenicline**, one of the anxiety events was coded as *anxiety disorder* PT; one of the depression events was coded as *major depression* PT; one of the amnesia events was coded as *memory impairment* PT; one of the emotional disorder events was coded as *emotional distress* PT; two of the panic attack events were coded as *panic disorder* PT and *panic reaction* PT respectively. For **bupropion**, one of the mood disorder events was coded as *mood altered* PT; one of the amnesia events was coded as *memory impairment* PT; one of the depression events was coded as *depressed mood* PT.

<sup>55</sup>For **varenicline** (n=3) two patients also experienced  $\geq 2$  other miscellaneous events, i.e depression and abnormal behavior (n=1) and agitation and mood swings (n=1). For **bupropion** (n=6), two patients also experienced  $\geq 1$  other miscellaneous event (feeling abnormal, n=1; memory impairment and disorientation, n=1). The remaining four patients experienced nervousness as the only miscellaneous event; one of these patients also had insomnia.

<sup>56</sup>Also experienced depression

<sup>57</sup>Full listing of reported events for varenicline is given in Appendix 5

Parameter		Varenicline (n=38) (380)	Bupropion (n=40) (80)
Insomnia	7 (70)	Insomnia	10 (20)
Irritability	5 (50)	Disturbance in attention	4 (8)
Nightmare	4 (40)	Irritability	4 (8)
Mental disorder	4 (40)	Crying	4 (8)
Paranoia	3 (30)	Psychomotor hyperactivity	3 (6)
<b>Psychiatric-related history</b>		n=25 (250)	n=20 (40)
No	9 (90)		12 (24)
Yes	16 (160)		8 (16)
Depression	7 (70)		3 (6)
Panic attacks	3 (30)		1 (2)
Anxiety	3 (30)		1 (2)
Bipolar	2 (20)		1 (2)
Suicide attempt	1 (10)		
Suicidality NOS	1 (10)		
Family history of suicide	1 (10)		
Post-traumatic stress disorder	1 (10)		
Nightmares	1 (10)		
Mood changes	1 (10)		
Mental disorder <sup>58</sup>	1 (10)		
Nervous disorder			1 (2)
Brain cancer <sup>59</sup>			1 (2)
<b>Concomitant medication</b>		n=38 (380)	n=40 (80)
Unknown	8 <sup>61</sup> (80)		8 (16)
No	2 (20)		4 (8)
Yes	28 (280)		28 (56)
Psychiatric-related	19 (190)		9 (18)
Benzodiazepine	12 (120)		4 (8)
Antidepressant	8 (80)		6 (12)
Antipsychotic	5 (50)		2 (4)
Sedative	2 (20)		1 (2)
Mood stabilizer/AED <sup>60</sup>	1 (10)		1 (2)
Antianxiety (buspirone)	1 (10)		
Other med(s) labeled for psychiatric event	16 (160)		17 (34)

<sup>58</sup>Also had history of violent dreams

<sup>59</sup>This patient was a 63 year-old male who experienced anxiety after taking bupropion; there was a positive dechallenge. Eleven days later, the patient was diagnosed with small lung cancer of the brain and lung; a craniotomy was done followed by chemotherapy.

<sup>60</sup>AED=antiepileptic drug

<sup>61</sup>In one report, for at least one of the concomitant non-psychiatric medications, the specific product name (generic or trade) was not given. If there were other listed medications, the medications were not psychiatric related and not labeled for the miscellaneous event(s).



Parameter	Varenicline (n=38) (380)	Bupropion (n=40) (80)
<b>Smoking information</b>		
Smoking status at time of event	n=5 (50)	n=7 (14)
Quit	3 (30)	3 (6)
Smoking	2 (20)	4 (8)
Smoking duration in years	n=1 (10)	n=15 (30); median 20 range 10-54
Number of packs per day (ppd)	n=2 (20); 1 and 3 ppd	n=2 (20); 1.25 and 3 ppd
Prior cessation attempt	n=4 <sup>62</sup> (40); bupropion (n=3) (30); nicotine [n=2 (20); patches, n=1 (10); lozenge n=1 (10)]	n=0 (0)
Enrolled in Get Quit (Pfizer support program or other)	2 <sup>63</sup> (20)	not applicable
<b>Significant change in behavior from past</b>		
New psychiatric experience	n=11 (110)	n=0 (0)
Psychiatric disease worsening	2 (20)	
Anxiety	9 (90)	
Depression	4 (40)	
Mania	2 (20)	
Panic attack	1 (10)	
Crying	1 (10)	
Sleep disorder	1 (10)	
<b>Substance/use abuse including alcohol</b>		
Alcohol	n=2 (20)	n=0 (0)
No use at any time	2 (20)	
No history of abuse		
History of use	2 (20)	
History of abuse		
Concomitant use		
Methamphetamine history of abuse	1 (10)	
<b>Outcome</b>		
Serious	38 (380)	12 (24)
Hospitalization	8 (80)	6 (12)
Life-threatening	1 (10)	1 (2)
Disability	1 (10)	2 (4)
Required intervention	2 <sup>64</sup> (20)	0 (0)
Other	33 (330)	6 (12)
Non-serious	0	28 (56)
<b>Recovery</b>		
Yes	n=23 (230)	n=26 (52)
Partial	11 (110)	25 (50)
No	1 (10)	1 (2)
	11 (110)	0 (0)

<sup>62</sup>Not mutually exclusive

<sup>63</sup>One patient was enrolled in the South Dakota Quit Hotline

<sup>64</sup>Each case reported at least one other serious outcome.

Parameter	Varenicline (n=38) (380)	Bupropion (n=40) (80)
<b>Dechallenge</b>	n=14 (140)	n=23 (46)
Positive	12 (120)	22 (44)
Negative	2 (20)	1 (2)
<b>Rechallenge, positive</b>	1 (2)	1 <sup>65</sup> (2)
<b>FDA received year</b>		
1997	0 (0)	20 (40)
1998	0 (0)	20 (40)
2006	10 (100)	0 (0)
2007	28 (280)	0 (0)
<b>Report type</b>		
Expedited	32 (320)	7 (14)
Periodic	0 (0)	0 (0)
Direct	6 (60)	33 (66)
<b>Reporter</b>		
Healthcare professional	17 (170)	8 (16)
Consumer	21 (210)	32 (64)
Solicited by sponsor	2 (20)	0 (0)

## 3.2 EPIDEMIOLOGY

### 3.2.1 Sponsor's information

#### 1. Clinical trial data

Pfizer provided a pooled analysis of selected psychiatric adverse events from their Phase II-III trial database. The results are displayed in table 3.2.1.1.

Pfizer noted that only two of the above events were considered serious (both in the psychotic disorders grouping). In general, bupropion was associated with higher event rates, while the nicotine patch group had only one event meeting these criteria (but the sample size for the nicotine patch was the smallest of all).

To place these data in context, it should be recalled that patients with psychiatric disorders were generally not enrolled in the varenicline clinical trials.

<sup>65</sup> A 56 year female (ISR# 3164572) experienced amnesia and difficulty thinking after taking bupropion (dose was 300 mg/day). Onset of event was unknown; therapy duration was 21 days. The patient discontinued therapy and had a positive dechallenge. The patient then had *two* subsequent rechallenges.

Table 3.2.1.1: Pooled analysis of adverse events in Phase II-III trials, for selected MedDRA High Level Group Terms involving psychiatric adverse events (Sponsor's 10-23-07 submission)

Treatment group	Varenicline (N)	Placebo (N)	Bupropion (N)	Nicotine patch (N)
Total subjects*	5,071	1,655	795	370
Total patient-years	1,192	355	130	60
Personality disorders & disturbances in behavior	297	82	46	1
Impulse control disorders	0	0	0	0
Disturbances in thinking and perception	18	2	4	0
Schizophrenia/psychotic disorders	2	1	0	0
	<b>(Rate/100 person-years)</b>			
Personality disorder	24.9	23.1	35.4	1.7
Disturbances in thinking and perception	1.5	0.6	3.1	0.0
Schizophrenia/psychotic disorders	0.2	0.3	0.0	0.0

\*These are pooled data from various trials with different comparator treatments

## 2. Postmarketing surveillance reports for varenicline (10-23-07 submission)

Pfizer conducted a review of spontaneous postmarketing reports they had received involving aggression or irrational behavior with varenicline, for the time period 5-10-06 to 9-5-07. To identify such reports, they reviewed cases mapping to the MedDRA High Level Group Terms (HLGT) for personality disorder/disturbance in behavior, disturbance in thinking/perception, and impulse control disorders; to the High Level Terms (HLTs) psychotic disorder, delusional disorder, and criminal activity, and to the Preferred Term (PT) abnormal behavior. This search yielded 525 case reports.

The 525 cases retrieved were reviewed and further classified as representing aggressive behavior (119 reports) or hallucinations/irrational behavior (159 reports). Of the aggressive behavior reports, 33 involved direct physical aggression against a person or object, and 86 involved verbal aggression, violent thoughts, or violent dreams. There was one report with a fatal outcome, the source for which was the news reports concerning a musician, Carter Albrecht, who was shot and killed by his neighbor after becoming violent while on varenicline. Alcohol was reported to be a factor in 3 of the aggressive actions reports, and pre-existing psychiatric disorders were present in about half the cases. Of the 159 cases involving hallucinations or irrational behavior, 126 involved hallucinations of various types, but the majority of these cases were poorly described. Some appeared to have occurred in patients without a previous history of psychosis. However, thirty-eight cases involved irrational behaviors; these appeared to reflect a variety of psychiatric symptoms.

On balance, Pfizer concluded that a small proportion of these cases potentially implicated varenicline but that psychiatric disorders are also associated with nicotine withdrawal, so that the effects of varenicline could not be distinguished from nicotine withdrawal. Although some cases occurred shortly after varenicline was discontinued, Pfizer interpreted that as inconsistent with a

causal relationship to varenicline (rather than raising the hypothesis of a varenicline withdrawal reaction).

### 3. Case reports in the literature of psychiatric disorders associated with varenicline

There have been published reports of schizophrenia (42-year-old female),<sup>66</sup> and mania (63-year-old male),<sup>67</sup> apparently exacerbated by varenicline. A third published report<sup>68</sup> described hypomania and suicidal ideation related to varenicline in a 41-year-old female, with history of bipolar II disorder and polysubstance abuse.<sup>69</sup> All three of these case reports were noted in the previous OSE consult regarding suicidal adverse events. A fourth case report, published in June of this year, describes a 50 year old woman with a past history of unipolar depressive disorder who was hospitalized for a manic episode after 3 months of varenicline treatment.<sup>70</sup> Varenicline was her only medication at the time. The authors noted that although the patient herself had no past history of mania, she did have a family history of bipolar disorder, and suggested that such a family history might be a risk factor for this type of adverse reaction.

#### 3.2.2 Literature Review

A total of 23 studies and case reports/series were identified and are summarized in the table 3.2.2.1 and 3.2.2.2 below with the purpose of assisting in understanding if smoking cessation alone may be associated with specific neuropsychiatric events; and examining whether preexisting mental illness matters in the risk of developing neuropsychiatric events after smoking cessation.

##### 3.2.2.1 Case Reports and Case Series

Eight case reports and case series comprised 18 patients who attempted smoking cessation using various interventions. As shown in Table 3.2.2.1, all cases occurred within a few weeks (a range from the first 24 hours to 6 weeks) after smoking cessation with the most common types of events reported in these studies as depressive episodes and symptoms, mania, and psychosis or psychotic episodes. Many cases (56%) had prior history of mental illness including schizophrenia, depression, and mania. The finding that most cases (78%) experienced depressive or other psychotic symptoms after they self-quit without pharmacotherapy suggests smoking cessation alone may be associated with worsening or inducing neuropsychiatric symptoms.

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<sup>66</sup>Freedman R. Exacerbation of schizophrenia by varenicline (letter). *Am J Psychiatry* 2007;164:1269.

<sup>67</sup>Kohen I, Kremen N. Varenicline-induced manic episode in a patient with bipolar disorder. *Am J Psychiatry* 2007;164:1269-70.

<sup>68</sup>Morstad AE, Kutscher EC, Kennedy WK, Carnahan RM. Hypomania with agitation associated with varenicline use in Bipolar II Disorder. *Annals of Pharmacotherapy*: epub 15 Jan 2008.

<sup>69</sup>Abstinent from alcohol and amphetamines for 3 months and 3 years respectively.

<sup>70</sup>Pumariega AJ, Nelson R, Rotenberg L. Varenicline-induced mixed mood and psychotic episode in a patient with a past history of depression. *CNS Spectr*. 2008;13:511-4.

<b>Table 3.2.2.1. Summary of Case Reports/Series Reporting Psychiatric Events after Smoking Cessation</b>					
Reference	No. of Cases	Intervention	Time of Exposure (TE)/ Onset of Event Postcessation (OEP)	Event	Pre-existing Mental Illness
Neumann 2004 <sup>71</sup>	1	Bupropion	5 days (TE)	Acute psychosis	Not Available
Dalack 1996 <sup>72</sup>	3	Case 1. Quit smoking on his own	2 days (TE)	Exacerbation of schizophrenic symptoms and anxiety	Chronic paranoid schizophrenia
		Case 2. Cut down on smoking	2-3 weeks (TE)	Increase in hostile and angry feeling (Severe hostility and moderately severe suspiciousness)	Chronic undifferentiated schizophrenia
		Case 3. Nicotine patch	2 weeks (TE)	Increase in hostility and delusional belief	Schizoaffective disorder
Bock 1996 <sup>73</sup>	3	A 12-week cognitive-behavior group treatment and supervised exercise program	Case 1. 11 days (OEP)	Reported feeling anxious, restless, and suicidal ideation. Symptoms markedly improved within 4 days of beginning nicotine patch.	A single episode of depressive symptoms
			Case 2. 1 week (OEP)	Increase in anxiety, anger, irritability, and marked anhedonia and negativism	History of alcohol dependence and a single episode of depressive symptoms
			Case 3. 6 weeks (TE), 3 weeks (OEP)	Increase in depressed mood, angry, tense, and irritability	No prior history of depression
Stage 1996 <sup>74</sup>	6	Case 1. Counseling	Within the first 24 hours (OEP)	Severe depressive symptoms including suicidal ideation and severe anxiety	A history of one major depressive episode
		Case 2. Counseling	2 weeks (OEP)	Depressive symptoms including dysphoric mood, disturbed sleep, feelings of worthlessness	A history of recurrent major depression

<sup>71</sup> Neumann M, Livak V, Paul HW. Acute psychosis after administration of bupropion (Zyban). *Psychiatr Prax.* 2004;31:140-141.

<sup>72</sup> Dalack GW, Healy DJ, Meador-Woodruff JH. Nicotine dependence and schizophrenia: Clinical phenomenon and laboratory findings. *Am J Psychiatry.* 1998;155:1490-1501.

<sup>73</sup> Bock BC, Goldstein MG, Marcus BH. Depression following smoking cessation in women. *Journal of Substance Abuse.* 1996;8:137-144.

<sup>74</sup> Stage KB, Glassman AH, Covery LS. Depression after smoking cessation: Case reports. *J Clin Psychiatry.* 1996;57:467-469.

Table 3.2.2.1. Summary of Case Reports/Series Reporting Psychiatric Events after Smoking Cessation					
Reference	No. of Cases	Intervention	Time of Exposure (TE)/ Onset of Event Postcessation (OEP)	Event	Pre-existing Mental Illness
		Case 3. Counseling	6 weeks (OEP)	Increasingly irritable and depressed	A history of bipolar disorder
		Case 4. Counseling and clonidine	5 days (OEP)	Sadness, loss of pleasure, and diminished energy	A history of one major depressive episode
		Case 5. Counseling	6 weeks (OEP)	Marked feelings of lethargy, loss of energy, and depressed mood	No history of any psychiatric illness
		Case 6. counseling	A few weeks (OEP)	Depressive symptoms. In spite of smoking again, patient experienced a full-blown episode of major depression and the depression persist after psychotherapy and pharmacotherapy	No history of major depression
Foulds 1995 <sup>75</sup>	1	Nicotine patch	1 month (TE)	Transient delusions and hallucination after smoking a cigarette	No history of psychiatric or drug abuse
Benazzi 1994 <sup>76</sup>	1	Stop abruptly on his own	1-2 weeks (OEP)	Psychotic affective disorder	A history of an episode of psychotic mania
Benazzi 1989 <sup>77</sup>	1	Stop abruptly on his own	Some days (OEP)	Gradual onset of severe mania	No history of psychiatric disorders
Labbate <sup>78</sup> 1992	2	Case 1. Stop abruptly on her own	1 week (OEP)	Gradual developed mania symptoms	No prior affective illness
		Case 2. Stop over 3 weeks on his own	2 weeks (OEP)	Became profoundly depressed and ruminated constantly about suicide	No prior mood disorder

<sup>75</sup> Foulds J, Toone B. A case of nicotine psychosis? *Addiction*. 1995;90:435-437.

<sup>76</sup> Benazzi F, Mazzoli M. Psychotic affective disorder after nicotine withdrawal. *Am J Psychiatry*. 1994;151:3.

<sup>77</sup> Benazzi F. Severe mania following abrupt nicotine withdrawal. *Am J Psychiatry*. 1989;146:12.

<sup>78</sup> Labbate LA. Nicotine cessation, mania, and depression. *Am J Psychiatry*. 1992; 149 (5): 708

### 3.2.2.2 Randomized Clinical Trials (RCT) and Observational Studies

Table 3.2.2.2 provides a summary of findings from relevant randomized clinical trials (RCT) (n=9) and observational studies (n= 6). The studies are presented by drug intervention in Table 2. Varenicline, bupropion, nicotine replacement therapy (NRT), fluoxetine, sertraline, clonidine, and cognitive-behavioral therapy have been used for the treatment of smoking cessation in those studies and trials. In one RCT<sup>79</sup> that used NRT as treatment for smoking cessation in heavy smokers with stable schizophrenia or schizoaffective disorder, there were no significant changes observed for positive symptoms or mood symptoms during 3 days of treated or untreated smoking abstinence. Gallagher<sup>80</sup> in an RCT and Addington<sup>81</sup> in a prospective follow-up study found no change in psychiatric events with NRT as a treatment option when compared to minimal or no treatment. Stapleton<sup>82</sup> et al. in a prospective cohort study that included varenicline as one of the treatment groups showed that participants who received treatment of varenicline had a significantly higher incidence rate of low mood/depression, anxiety/panic, disturbed sleep, vivid dreams and all other adverse reaction measures except skin irritation compared to patients in the NRT group despite the fact that a lower percentage of participants in varenicline group had current mental health disorders. Although there was no report of exacerbation of mental illness symptoms by varenicline, this study did report symptoms of severe psychological reaction including anxiety, paranoia, confusion, and impaired motor control in one patient with a history of mental health problems. In this study, 25.5% of varenicline-treated patients and 28.9% of NRT-treated patients had current mental illness. Two RCTs<sup>83, 84</sup> that included bupropion as active treatment for smoking cessation found no significant or little effect of bupropion on positive or negative symptoms and depression when compared to placebo. The incidence rates of Major Depressive Disorder (MDD) ranged from 0.49% to 2.7% in other trials that assessed bupropion for the treatment of smoking cessation (Patten, Killen 2004)<sup>11, 85</sup>. The majority (50% to 75%) had a history of prior mental illness and MDD cases were seen in both the treated and placebo group. Two RCTs<sup>86, 87</sup> and one prospective follow-up study<sup>88</sup> found the risk of MDD after treatment with antidepressant including SSRI and TCA for smoking cessation ranged from 4% to 16.7%.

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<sup>79</sup> Dalack GW, Becks L, Hill E, Pomerleau OF, Meador-Woodruff JH. Nicotine withdrawal and psychiatric symptoms in cigarette smokers with schizophrenia. *Neuropsychopharmacology*. 1999;21:195-202.

<sup>80</sup> Gallagher SM, Penn PE, Schindler E, Layne W. A comparison of smoking cessation treatments for persons with schizophrenia and other serious mental illnesses. *J Psychoactive Drugs*. 2007;39:487-497.

<sup>81</sup> Addington J, el-Guebaly N, Campbell W, Hodgins DC, Addington D. Smoking cessation treatment for patients with schizophrenia. *Am J Psychiatry*. 1998;155:974-976.

<sup>82</sup> Stapleton JA, Watson L, Spirling LI, et al. Varenicline in the routine treatment of tobacco dependence: a pre-post comparison with nicotine replacement therapy and an evaluation in those in mental illness. *Addiction*. 2007; 103: 146-154.

<sup>83</sup> Evins AE, Deckersbach T, Cather C, et al. Independent effects of tobacco abstinence and bupropion on cognitive function in schizophrenia. *J Clin Psychiatry*. 2005;66:1184-1190.

<sup>84</sup> Patten CA, Rummans TA, Croghan IT, et al. Development of depression during placebo-controlled trials of bupropion for smoking cessation: Case reports. *J Clin Psychiatry*. 1999; 60(7): 436-441.

<sup>85</sup> Killen JD, Robinson TN, Ammerman S, et al. Major depression among adolescent smokers undergoing treatment for nicotine dependence. *Addictive Behaviors*. 2004;29:1517-1526.

<sup>86</sup> Borrelli B, Niaura R, Keuthen NJ, et al. Development of major depressive disorder during smoking-cessation treatment. *J Clin Psychiatry*. 1996;57:534-538.

<sup>87</sup> Killen JD, Fortmann SP, Schatzberg A. Onset of major depression during treatment for nicotine dependence. *Addictive Behaviors*. 2003;28:461-470.

One RCT<sup>89</sup> and two observational studies<sup>15, 90</sup> attempted to compare depressive outcomes of those who achieved smoking abstinence versus those who did not, but the results of these studies were not consistent. Kahler<sup>16</sup> et al. found that abstinence from smoking was associated with short-term and long-term reduction of depressive symptoms in a RCT. However, Glassman<sup>17</sup> et al found that those continued to smoke had a lower incidence rate (6%) of developing MDD compared with those who stopped smoking (31%) in a 6 month follow-up study. In another prospective follow-up study, Tsoh<sup>15</sup> found there was no difference in risk of depressive episodes in patients who achieved abstinence from smoking and those continued to smoke. George<sup>91</sup> et al did not found statistically significant effects of smoking abstinence with bupropion or nicotine patch on positive or negative symptoms of depression among smokers with stable schizophrenia.

Three RCTs and five observational studies have reported the risk of MDD among patients with and without a history of MDD. Among them, two RCTs and four observational studies have found higher incidence rates of depressive symptoms among patients who had a history of MDD than those without (Patten, Tsoh, Borrelli, Glassman, Covey, Niaura)<sup>11, 13, 15, 17, 92, 93</sup>. Covey<sup>19</sup> et al reported that as many as 30% of subjects with recurrent major depression experienced new episodes of depression after smoking cessation. In contrast, the incidence of new onset depression among those with no history of depression was 2% in the same study. In the Tsoh study<sup>15</sup>, MDD rate was higher in patients with a history of depression (24%) compared to those with no history (10%). However, the type of adverse reactions observed among patients with mental illness who received varenicline did not differ significantly from those without mental illness in a prospective cohort study (Stapleton)<sup>9</sup> although the incidence rate was higher in the varenicline treated group compared to NRT treated patients. Similarly, one RCT among adolescent smokers found that one out of two (50%) cases of MDD had a history of depression (Killen 2004)<sup>12</sup>.

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<sup>88</sup> Tsoh JY, Humfleet GL, Munoz RF, Reus VI, Hartz DT, Hall SM. Development of major depression after treatment for smoking cessation. *Am J Psychiatry*. 2000;157:368-374.

<sup>89</sup> Kahler CW, Brown RA, Ramsey SE, et al. Negative mood, depressive symptoms, and major depression after smoking cessation treatment in smokers with a history of major depressive disorder. *Journal of Abnormal Psychology*. 2002;4:670-675.

<sup>90</sup> Glassman AH, Covey LS, Stetner F, Rivelli S. Smoking cessation and the course of major depression: A follow-up study. *Lancet*. 2001;357:1929-1932.

<sup>91</sup> George TP, Vessicchio JC, Sacco KA, et al. A placebo-controlled trial of bupropion combined with nicotine patch for smoking cessation in schizophrenia. *Biol Psychiatry*. 2008; 63: 1092-1096.

<sup>92</sup> Covey LS, Glassman AH, Stetner F. Major depression following smoking cessation. *Am J Psychiatry*. 1997;154:263-265.

<sup>93</sup> Niaura R, Britt DM, Borrelli B, Shadel WG, Abrams DB, Goldstein MG. History and symptoms of depression among smokers during a self-initiated quit attempt. *Nicotine Tob Res*. 1999;1:251-257.



Table 3.2.2.2 Summary of RCTs and Observational Studies Reporting Psychiatric Outcomes with Smoking Cessation								
Reference	Study Design	Study Population	Exclusion Criteria	n	Intervention	Control	Duration	Results
Stapleton <sup>83</sup> 2007	Prospective cohort study	Patients attended the South London and Maudsley NHS Foundation Trust Specialist Tobacco Dependence Clinic between May 2006 and April 2007. 25.5% (Varenicline) vs. 28.9% (NRT) had current mental illness.	No pts were excluded from using NRT;  Pts with severe renal function impairment, under 18 yrs, or trying to conceive were excluded from varenicline group.	412	Group support sessions +  NRT (patch, nasal spray, gum, lozenge, inhalator, or microtab)  Group support sessions +  Varenicline	Participants in NRT group	12 weeks	Compared with the Varenicline group, the NRT group had significantly higher rates of disturbed sleep, vivid dreams, headache, low mood, anxiety/panic, disorientation, and all other measures of psychiatric irritation.  One report in Varenicline group of severe psychological symptoms including anxiety, confusion, and impaired concentration.  Slightly higher incidence of disturbed sleep, low mood, confusion, vivid dreams, anxiety/panic in Varenicline cohort who had mental illness compared to those in NRT group.
Evins <sup>84</sup> 2005	RCT	Adult smokers w/schizophrenia or schizoaffective disorder, depressive type, had stable psychiatric symptoms and had been on a stable dose of antipsychotic medication for 30 days	Current MDD, depression HAM-D score <20, history of mania, substance abuse	53	Bupropion + cognitive-behavioral therapy	Placebo + cognitive-behavioral therapy	12 weeks	No detectable worse performance on a neuropsychological test or clinical symptoms of tobacco abstinence.

Table 3.2.2.2 Summary of RCTs and Observational Studies Reporting Psychiatric Outcomes with Smoking Cessation									
Reference	Study Design		Study Population	Exclusion Criteria	n	Intervention	Control	Duration	Results
George <sup>92</sup> 2008	RCT		Smokers w/schizophrenia or schizoaffective disorder on stable doses of antipsychotic drugs for at least 1 month	Psychiatric instability including active suicidal or homicidal ideation, alcohol or illicit drug abuse	58	Bupropion + Nicotine patch	Placebo + Nicotine patch	10 weeks	No statistically significant difference of smoking abstinence between bupropion on positive (psychiatric) symptoms and depression.
Patten <sup>85</sup> 1999	RCT 1		Smokers at least 18 years of age (17.6% had a history of past MDD)	Unstable psychiatric illness	205	Bupropion	Placebo	7 weeks	At wk 4, 1 (0.49%) developed MDD in bupropion group; none in placebo group; history of MDD.
	RCT2	Phase1	26.6% had a history of past MDD	Unstable psychiatric illness	252	Bupropion	none	7 weeks	no case of MDD
		Phase2	Those abstinent from smoking in phase 1 (25.7% had a history of past MDD)	Unstable psychiatric illness	148	Bupropion	Placebo	45 weeks	During wk 9-44, 4 cases developed MDD. Bupropion group: 1 case; Placebo group: 3 cases (75%) had history of MDD
Killen <sup>86</sup> 2004	RCT		Adolescent smokers aged 14-18 (11% w/h/o a past episode of MDD)	Bipolar disorder, schizophrenia, current depression, substance abuse	211	Nicotine patch + Bupropion	Nicotine patch + placebo	9 weeks	2 participants (1%) developed MDD. One out of 10 had a history of MDD.
Dalack <sup>80</sup> 1999	RCT		Heavy smokers with stable Schizophrenia or schizoaffective disorder for at least 3 months	Current non-nicotine substance abuse	19	Transdermal NRT patch	Placebo patch	12 days	Neither positive symptoms nor mood symptoms changed

Table 3.2.2.2 Summary of RCTs and Observational Studies Reporting Psychiatric Outcomes with Smoking Cessation								
Reference	Study Design	Study Population	Exclusion Criteria	n	Intervention	Control	Duration	Results
Gallagher <sup>81</sup> 2007	RCT	Smokers with schizophrenia and other serious mental illness		181	Contingent reinforcement; Contingent reinforcement + NRT patch for 16 wks	Minimal intervention, self-quit control group	36 weeks	No evidence of psychiatric exacerbation
Addington <sup>82</sup> 1998	Prospective follow-up study	Smokers aged 18-65 years w/schizophrenia	Substance abuse or dependence other than nicotine	50	Nicotine patch + Cognitive-behavior group program	none	6 months	No change in positive symptoms of schizophrenia observed
Tsoh <sup>89</sup> 2000	Prospective follow-up study	Smokers aged 18-65 years	Subjects taking psychoactive drugs or undergoing psychiatric treatment, episodes of MDD within 3 months	304	Psychological group intervention + Nicotine gum  Psychological group intervention + Nortriptyline	Psychological group intervention + placebo	12 months	12-month incidence of MDD episode: 11.5% in Nicotine group. 16.4% in Nortriptyline group.  14.7% in those who achieved abstinence; 13.4% in those who did not achieve abstinence.  23.7% in patients with history of depression; 9.7% in those without history of MDD.
Killen <sup>88</sup> 2003	RCT	Smokers age > 18 (20% w/h/o a past episode of MDD)	Bipolar disorder, schizophrenia, current depression, substance abuse	224	Nicotine patch + paroxetine 20mg;  Nicotine patch + paroxetine 40mg	Nicotine patch + placebo	9 weeks	4% (n=10) experienced psychiatric cases emerged at 4 weeks Placebo group: 5 cases emerged at 1 week Paroxetine 20mg group: 5 cases emerged at 1 week Paroxetine 40mg group: 5 cases emerged at 1 week

Table 3.2.2.2 Summary of RCTs and Observational Studies Reporting Psychiatric Outcomes with Smoking Cessation								
Reference	Study Design	Study Population	Exclusion Criteria	n	Intervention	Control	Duration	Results
Borrelli <sup>87</sup> 1996	RCT	Smokers aged 18-65 years without current MDD (32% had a history of MDD)	Bipolar disorder, current psychiatric illness, suicidal ideation	69	Fluoxetine 30mg Fluoxetine 60mg	Placebo	10 weeks	5 (7%) met threshold for MDD: Placebo group: 1 case Fluoxetine 30mg: 4 cases Fluoxetine 60 mg: 0 cases  Cases had significantly higher depression score at 10 weeks than those who did not have MDD after smoking cessation
Glassman <sup>91</sup> 2001	Prospective follow-up study	Smokers with a history of MDD, but no current depression in the past 6 months	Bipolar disorder	100	Sertraline or Placebo	Participants who continued to smoke	6 months	Those continued to smoke (6%) had developed MDD  Those who stopped smoking 13(31%) had developed MDD during 6 month follow-up  Smokers with a history of depression who abstain from smoking are at significantly increased risk of developing a new episode of MDD
Covey <sup>93</sup> 1997	Prospective follow-up study	Adult smokers who successfully completed a 10-wk smoking cessation program with no current diagnosis of MDD or history of any psychotic illness.		126	Clonidine	NA	3 months	3-month incidence of MDD  No history of MDD  History of a single episode of depression: 17%,  History of recurrent depression: 30%.
Niaura <sup>94</sup> 1999	Prospective cohort	Smokers w/ and w/o h/o MDD	Any organic, psychiatric, or substance abuse problems	133	No intervention (Smokers with a history of MDD)	No intervention (smokers without a history of MDD)	4 weeks	Those with history of MDD had significantly more depressive symptoms;  Those without history of MDD had significantly fewer depressive symptoms

Table 3.2.2.2 Summary of RCTs and Observational Studies Reporting Psychiatric Outcomes with Smoking Cessation								
Reference	Study Design	Study Population	Exclusion Criteria	n	Intervention	Control	Duration	Results
Kahler <sup>90</sup> 2002	RCT	Smokers aged 18-70 years, w/h/o MDD	Current MDD or other Axis I disorder, current user of psychotropic medication or psychotherapy, current non-nicotine abuse,	179	Treatment incorporating cognitive-behavioral therapy for depression	A program including self-monitoring, self-management, nicotine fading, relapse prevention, and social support	6 weeks of tx with 2-week of follow-up after quitting smoking	15.3% had incident depression. Continuous abstinence associated with short-term reductions in depressive symptoms.

### 3.2.3 Reporting rates

Reporting rates for both Zyban and Chantix, for the events of interest are presented in Table 3.2.4.1.

Table 3.2.4.1. U.S. reporting rates for psychosis and aggression events, first 14 months of marketing

Drug Product	Time period	Total RXs*	All psychosis reports received (n)	All aggression reports received (n)	All psychosis reports / 100,000 Rx	All aggression reports/ 100,000 Rx
Zyban (Z)	5/15/97 to 7/5/98	2,120,000	11	8	0.5	0.4
Chantix (C)	5/10/06 to 8/31/07	5,466,000	98	48	1.8	0.9
Reporting Ratio (C/Z)					3.4	2.3

\*Source: Verispan, LLC: Vector One®: National (VONA).

During the first 14 months of marketing, varenicline had the largest number of reports for psychosis and aggression, both in terms of absolute numbers and in the proportion to prescriptions filled. This is made clear by the reporting rate ratios, displayed in the bottom row. Varenicline had threefold greater reporting for psychosis and twofold greater reporting for aggression.

### 3.2.4 Disproportionality analysis

Tables 3.2.4.1 and 3.2.4.2 show the greater than expected EBM scores and confidence intervals for Psychosis. Although both varenicline and bupropion have greater-than-expected scores for hallucination and paranoia, varenicline has a greater-than-expected scores for other psychotic events such as bipolar disorder, mania, schizophrenia, and psychotic disorders.

Table 3.2.4.1 Varenicline (suspect drug) Psychosis reports – Cumulative Signal EBM Scores through 2007 (with EB05 > 2)

MedDRA Preferred Term	N	E	RR	EB05	EBGM	EB95
Paranoia	55	6.4	8.6	6.1	7.7	9.6
Bipolar disorder	32	3.7	8.6	5.2	7.1	9.6
Mania	41	5.7	7.2	4.8	6.3	8.1
Psychotic disorder	46	8.4	5.5	3.9	5	6.3
Delusion	22	3.2	6.8	3.8	5.4	7.6
Hallucination	59	15.8	3.7	2.9	3.5	4.4
Hallucination, auditory	18	4.0	4.5	2.5	3.7	5.4
Schizophrenia	10	1.5	6.6	2.5	4.3	7.1

Table 3.2.4.2 Bupropion (suspect drug) Psychosis reports, Cumulative Signal EBGM Score through 2007 (with EB05 >2)

MedDRA Preferred Term	N	E	RR	EB05	EBGM	EB95
Hallucination, visual	24	4.9	4.9	3	4.2	5.8
Hallucination	85	28.7	3	2.4	2.9	3.4
Paranoia	41	12.4	3.3	2.4	3.1	4

Tables 3.2.5.3 and 3.2.5.4 also show greater-than expected EBGM scores and confidence intervals for aggression with both products. Varenicline, unlike bupropion, also shows a greater-than-expected score for violence and hostility.

Table 3.2.4.3: Varenicline (suspect drug) - Aggression - Cumulative Signal EBGM Score through 2007 (with EB05 > 2)

MedDRA Preferred Term	N	E	RR	EB05	EBGM	EB95
Homicidal ideation	43	2.4	17.7	12.9	17.1	21.9
Anger	130	9.0	14.5	12.2	14.3	16.5
Aggression	126	14.5	8.7	7.1	8.3	9.6
Violence-related symptom	14	0.8	16.9	6.3	12.6	22.7
Hostility	11	1.2	8.9	3.2	5.4	9.0

Table 3.2.4.4: Bupropion (Suspect drug) Aggression, Cumulative Signal EBGM Score through 2007 (with EB05 > 2)

PT	N	E	RR	EB05	EBGM	EB95
Aggression	153	25.6	6.0	5.1	5.8	6.6
Homicidal ideation	11	1.7	6.4	2.6	4.4	7.0
Anger	29	9.0	3.2	2.2	3.0	4.0

Although both products show greater-than-expected scores for MedDRA preferred terms (PT) indicating panic, mood changes and abnormal feelings (Tables 3.2.4.5 and 3.2.4.6), varenicline has more varied reports than bupropion. And although varenicline had high scores for depression, bupropion had more greater-than-expected scores for other PTs indicating depression including Major Depression. Varenicline had greater-than-expected scores for stress and emotional disorder.

Table 3.2.4.5: Varenicline (suspect drug) - Miscellaneous Psychological Conditions Cumulative Signal EBGM Score through 2007 (with EB05 > 2)

MedDRA Preferred Term	N	E	RR	EB05	EBGM	EB95
Personality change	43	3.2	13.3	8.9	12.2	16.2
Emotional disorder	54	5.1	10.5	7.3	9.4	12
Panic attack	96	10.9	8.8	6.9	8.3	9.8

Table 3.2.4.5: Varenicline (suspect drug) - Miscellaneous Psychological Conditions Cumulative Signal EBGM Score through 2007 (with EB05 > 2)

MedDRA Preferred Term	N	E	RR	EB05	EBGM	EB95
Thinking abnormal	55	6	9.2	6.5	8.2	10.4
Mood swings	60	6.7	8.9	6.4	8	10
Sleep disorder	80	9.7	8.3	6.3	7.7	9.2
Stress	54	6.7	8	5.7	7.2	9
Nervousness	96	13.9	6.9	5.5	6.5	7.7
Depression	388	67.3	5.8	5.2	5.7	6.2
Mood altered	38	5.7	6.7	4.5	5.9	7.6
Panic reaction	19	2.2	8.6	4.3	6.3	9.3
Anxiety	254	56.5	4.5	4	4.4	4.9
Feeling of despair	13	1.3	10.3	3.9	6.5	10.8
Fear	32	5.7	5.6	3.6	4.9	6.5
Negative thoughts	8	0.5	16.5	3.6	7.8	20.3
Agitation	77	17.9	4.3	3.4	4.1	4.9
Disorientation	49	12	4.1	3	3.8	4.8
Feelings of worthlessness	7	0.5	15.3	3	6.3	16.7
Depressed mood	31	7.2	4.3	2.8	3.9	5.1
Sleep terror	7	0.5	12.8	2.7	5.5	11.8
Panic disorder	8	1.1	7.3	2.3	4.2	7.3

Table 3.2.4.6: Bupropion (Suspect drug) - Miscellaneous Psychological Conditions, Cumulative Signal EBGM Score through 2007 (with EB05 > 2)

PT	N	E	RR	EB05	EBGM	EB95
Depressed mood	38	4.8	7.9	5.1	6.8	8.8
Major depression	23	2.6	8.9	4.8	6.9	9.8
Agitation	254	51.3	4.9	4.4	4.9	5.4
Personality change	29	4.1	7.1	4.3	5.9	8
Panic reaction	17	2.4	7.1	3.5	5.3	7.8
Tension	13	1.7	7.8	3.3	5.3	8.2
Feeling abnormal	158	43.2	3.7	3.1	3.6	4.1
Tearfulness	11	1.3	8.3	3.1	5.2	8.5
Nervousness	157	44.6	3.5	3	3.5	3.9
Panic attack	46	11.5	4	2.9	3.7	4.7
Disorientation	80	23	3.5	2.8	3.4	4
Sleep disorder	50	13.6	3.7	2.7	3.5	4.4
Anxiety	299	103.8	2.9	2.6	2.9	3.1
Mood swings	40	11.9	3.4	2.4	3.2	4.1

In sum, both drugs showed disproportionate reporting for a number of the MedDRA Preferred Terms of interest, but the disproportion was frequently greater for varenicline compared to



bupropion particularly with respect to violence, hostility, psychotic disorder including bipolar disorders, mania, and schizophrenia, stress, and emotional disorders.

### 3.2.5 Additional clinical trial information

On July 9, 2008, the House Committee on Veterans' Affairs held a hearing concerning a Veterans Administration (VA) study of smoking cessation treatment that included varenicline as one of the treatment options. It should be noted that this was not a randomized drug trial. Nonetheless, the data regarding adverse psychiatric events with varenicline treatment may provide some insights into the potential for varenicline to induce such reactions. According to the testimony by Secretary James B. Peake, M.D., study CSP-519 involved patients with post-traumatic stress disorder (PTSD) who were attempting to stop smoking. In study CSP-519, there were 241 patients who were treated with varenicline, and 704 who were not. "Significant psychiatric adverse effects" reportedly occurred in 7.9% of the patients treated with varenicline (19/241) and in 4.0% of the patients who did not receive varenicline (28/704). At present, few additional details are available regarding the data from this study; OSE plans to try to contact the VA study team directly to obtain more information.

## 4 DISCUSSION

### 4.1 AERS CASES

As noted in Section 2.1 and 3.1 above, AERS reports of psychoses, aggression, and miscellaneous psychiatric events were considered for review. The psychosis and aggression groups combined encompassed the minority (varenicline 25%; bupropion 14%) of the reports and all of them were hands on reviewed. Since the majority (varenicline 75%; bupropion 86%) of reports were in the *miscellaneous* psychiatric event group, to create a more manageable case series, only a random sample of reports were manually reviewed for the miscellaneous events. It is assumed that the case profiles for these events apply to the entire group sampled. Appendix 2 shows the balance between the sample and the entire group for varenicline and bupropion.

The profile of the case series (n=243) was different than the crude counts (n=753) in that proportions for reports with miscellaneous psychiatric event reports were lower and mania/psychosis- and aggression-reports were higher.<sup>94</sup> However, this case series of 243 individually reviewed reports actually represents a *larger* population because of the *sampling* for the miscellaneous reports. With this adjustment<sup>95</sup> (shown in Table 3.1.1 and 3.1.2) the case series can be considered to be 625 reports with similar composition to the original crude count: *mostly varenicline* (84%; vs. bupropion 16%) and *mostly miscellaneous psychiatric event cases* for both drugs (varenicline 80%; bupropion 81%).

#### 4.1.1 Psychosis/mania

The proportion of all varenicline reports that were *psychosis/mania* (98/526; 19%) was higher than for bupropion (11/99; 11%),<sup>96</sup> both still represented a small amount of the entire case series.

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<sup>94</sup>For varenicline (n=184) proportions for psychosis/mania, aggression and miscellaneous were 53, 26 and 21 percent respectively. For bupropion (n=59) proportions for psychosis/mania, aggression and miscellaneous were 19, 14, and 68 percent respectively (may not exactly add to 100% due to rounding). See section 2.1.4

<sup>95</sup>Miscellaneous psychiatric cases increased x 10 for varenicline and x 2 for bupropion.

<sup>96</sup>The denominators for varenicline (526) and bupropion (99) take into account the sampling (miscellaneous) that was done for this consult.

For both groups, most (82%) of the patients reported only one psychosis/mania event.<sup>97</sup> For varenicline, hallucination (labeled as ‘rare’) was the most common (42%) event reported.<sup>98</sup> Most (30/38<sup>99</sup>) of the patients reported hallucination as the only event. In the remaining eight patients, the hallucinations were reported with other psychosis/mania events such as psychotic disorder, paranoia, delusion, and bipolar disorder. Paranoia (labeled as ‘rare’) was the second most common (20%) reported event. Most (13/20) of the patients reported paranoia as a single event and the remainder (7/20) reported other psychosis/mania events (e.g. psychotic disorder and bipolar disorder) in addition to paranoia. The third most commonly reported event was bipolar disorder (16%; not labeled), and in most (10/16) of these cases, the patient’s pre-existing bipolar disorder worsened after varenicline exposure; in the remaining 6 cases, the bipolar disorder was a new event. Varenicline had a higher (28%) proportion of reports than bupropion (9%) where there was a mention that following drug exposure, a significant change in behavior occurred.

Similar to the varenicline cases, most (81%) of the bupropion patients reported a single event. The most commonly reported event was paranoia (5) (‘paranoid ideation’ labeled); in 3 of the 5 cases, paranoia was the only reported event. Two other cases reported hallucination (labeled) and psychotic disorder (not labeled) in addition to paranoia. The second most commonly reported event was psychotic disorder and most (2/3) of these patients did not report another event; the third patient also reported paranoia.

By median age, the patients in the bupropion case series were 10 years older (58 years) than those in the varenicline case series (48 years). Regarding gender, the cases involved more females than males in both drug groups (varenicline 65%; bupropion 73%).<sup>100</sup> An association between the psychosis-mania event(s) and varenicline and bupropion was noted by a temporal relationship and positive dechallenge from the drugs. There was a short median time to onset of events of 6 and 4 days for varenicline and bupropion, respectively and a positive dechallenge in more than a third (38%) of the varenicline cases and in approximately three-quarters (73%) of the bupropion cases. Varenicline reported more cases with a serious outcome (96%) than bupropion (36%). There were more hospitalizations with varenicline (14%) than bupropion (9%). Although less varenicline patients reported recovery from their event(s) (40%) vs. bupropion (63%), a large proportion of varenicline cases (39%) did not report whether the patient recovered.

There were 17% and 28% of patients that reported negative psychiatric history prior to taking varenicline and bupropion, respectively. More than half (53%) of the varenicline patients reported a positive psychiatric history vs. 18% for bupropion. However, there was a higher proportion of bupropion (54%) than varenicline (30%) patients where psychiatric history was unknown. The most common psychiatric history was bipolar disorder for both drugs; the second most common for varenicline was depression. In most of the varenicline patients that had a significant change(s) from the past, the change was a disease worsening; bipolar disorder was the most common disease that worsened. Very few patients in either group reported taking no concomitant medications (varenicline 4%; bupropion 0%). The concomitant use of one or more psychiatric medications was reported more for varenicline (59%) than for bupropion (21%).<sup>101</sup>

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<sup>97</sup>Unless otherwise stated any mention of ‘other events’ within the three event groups (psychosis/mania; aggression; miscellaneous) means events *within* these respective classes.

<sup>98</sup>Numbers (or proportions) of patients mentioned for commonly reported psychosis/mania events for varenicline and bupropion are not mutually exclusive because some patients experience *more* than one such common event(s).

<sup>99</sup>Three varenicline patients reported *two different types* of hallucinations. Because these events related to the same event (hallucination), they are not considered to have reported multiple events.

<sup>100</sup>May be related to smaller population for bupropion compared to varenicline.

<sup>101</sup>Concerning concomitant medication, the bupropion group had more unknown (72%) than the varenicline group (22%).

Antidepressants were the single most common psychiatric concomitant medication for varenicline; for bupropion, antidepressants, antipsychotics, and mood stabilizers were equally common.

Smoking status at the time of the event(s) was not provided in most of the varenicline cases (78%) and in all of the bupropion cases (100%). Where known (n=22), the patients were equally divided between smoking and not smoking at the time of the event in the varenicline group; there was no mention of nicotine withdrawal in the 11 patients who were not smoking at the time of varenicline therapy. Among the patients with unknown smoking status in the varenicline group, there were two patients who thought that their events (hallucinations and mania, respectively) were related to nicotine withdrawal although there was no specific mention of quitting or tapering their cigarette smoking.

There was very little mention of alcohol (or any other substance of abuse). The status of alcohol use was mentioned more in the varenicline group (15/98; 15%) than the bupropion group (1/11; 9%). There were three varenicline patients with concurrent use of alcohol. Two patients, who both had a regular wine intake of 1-2 glasses per day experienced paranoia after 2-3 days of starting Chantix; concomitant medications were hydrocodone and alprazolam, respectively. The third patient started taking Chantix, drank four glasses of wine, and experienced hallucination; fluoxetine was a concomitant medication.<sup>102</sup> For bupropion, only one case mentioned a history of alcohol abuse (events were *paranoia* and *hallucination*).

#### 4.1.2. Aggression/hostility

Patients that reported aggression/hostility represented a small proportion of all cases for varenicline (48/526; 9%) and bupropion (8/99; 9%). For both groups, most of the patients reported just one aggression event (varenicline 79%; bupropion 89%). For varenicline, aggression (labeled, as 'infrequent') and or anger (not labeled) were the first and second most commonly reported events (n=36; 75%). Seven of these 36 patients, also reported homicidal ideation (not labeled; discussed below). In the remaining 29 non-homicidal patients, no physical harm was done to another person. Of the 29 patients, two exhibited abnormal automobile driving behavior (described as 'road rage' and 'manically' respectively).

The proportion of the particular aggression-events was different for bupropion vs. varenicline. For bupropion, there was more hostility (labeled as 'infrequent') reported (63%) and less aggression (labeled) and anger (not labeled)—the opposite of varenicline. Due to the small number of bupropion cases (n=8) compared to varenicline (n=98), no inferences can be made. For the purposes of this review, the events of *hostility*, *aggression*, and *anger* were considered similar behaviors. The most significant difference for bupropion was the lack of any *homicidal ideation* which was frequently seen (19/48) with varenicline. Like varenicline, among the eight bupropion cases, there was no mention that any others were harmed. Similar to the psychosis/mania groups, varenicline had a higher (33%) proportion of reports than bupropion (none) where there was mention that following exposure, a significant change from the past had taken place. Most (12/16) of the varenicline-significant changes in behavior from the past were new experiences (vs. worsening of pre-existing disease).

The bupropion patients (median 54) were older than those of varenicline (median 48) but the difference was not as great as seen with the psychosis/mania groups. Like the psychosis/mania groups, there was a female predominance for varenicline and bupropion (73% and 87% respectively).

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<sup>102</sup>This case was coded as *alcohol interaction* PT

An association between the aggression event(s) and varenicline and bupropion was noted by a temporal relationship and positive dechallenge from the drugs. There was a short median time to onset of 7 days for each drug respectively and a positive dechallenge in 23% of the varenicline and all<sup>103</sup> of the bupropion cases. While all of the varenicline cases were reported as serious, only one-quarter (2/8) of the bupropion cases were reported as serious (life-threatening n=1; other n=1). For varenicline, there were very few (2/48; 4%) patients with outcomes *besides* 'other.' One-half of the varenicline patients recovered from their event(s); recovery was more than half (63%) for bupropion.

About one-third (33%) of the varenicline patients and 13% of the bupropion patients had no prior reported psychiatric history. One-quarter of the varenicline patients had reported prior psychiatric history. In most (88%) of the bupropion patients, prior psychiatric history was unknown. The two most common psychiatric histories for varenicline were bipolar disorder and depression (similar to the psychosis/mania groups).

A minority of the patients for both drug groups reported taking no concomitant medications (varenicline 13%; bupropion 25%). Concomitant psychiatric medication use was reported in almost two-thirds (65%) for varenicline patients and half (50%) for bupropion patients. The most commonly reported concomitant psychiatric medications for varenicline were antidepressants (similar to the psychosis/mania groups).<sup>104</sup>

*Homicidal ideation* was reported in 18 cases for the varenicline aggression group and is a cause for concern. In 12 of the 18 cases, the patient had no specific person in mind and no homicide was contemplated or planned. In the remaining cases, where information was reported<sup>105</sup> (n=5), there was a specific person mentioned as a target. In three cases, the patient wanted to kill their spouse, but there was no actual action taken. Another patient 'swung' at her mother (who was in her 90's) and missed; she then continued to take her rage out by destroying other inanimate objects in her house. The last patient was 'ready to kill someone;' she had a gun next to her bed and dreamt that she shot her husband (which she did not).

The smoking status at the time of the event(s) was mostly unknown (varenicline 69%; bupropion 88%). Where known, the varenicline (n=15) patients were about equally divided between smoking (n=8) and not smoking (n=7);<sup>106</sup> there was one bupropion patient who had quit smoking. For all the known non-smoking (at time of event) patients for both drug groups, there was only one mention (or recognition) that the patient was experiencing nicotine withdrawal at the time of the event: this was the bupropion patient (experienced aggression) who felt that the drug 'increased her withdrawal symptoms.'

There was limited mention (8%) of alcohol for the varenicline group and none for bupropion. Of the mentions of alcohol use, only one reported concomitant use (varenicline). This was 58-year-old female (history of alcoholism and hepatitis C) who experienced an increased urge to drink. She had a blackout while drinking alcohol and became combative. She claimed 'it was hard for her liver to metabolize since it has hard liquor like vodka.'

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<sup>103</sup>May be related to the smaller population for bupropion compared to varenicline.

<sup>104</sup>Concomitant psychiatric medication was only known for 1 bupropion patient (antidepressant and benzodiazepine).

<sup>105</sup>In one report of homicidal ideation, there was no information given for any further assessment as to whether a specific person (to kill) existed.

<sup>106</sup>Smoking status was known for only one bupropion patient who had quit.

### 4.1.3 Miscellaneous

Patients who reported miscellaneous psychiatric events were the highest proportion of all the event groups for varenicline (380/526; 72%) and bupropion (80/99; 81%). This was not surprising in that the adverse event search criteria for the miscellaneous psychiatric events were broader than either the psychosis/mania or the aggression search terms (Section 2.1.1.1). There was a higher proportion (47%<sup>107</sup>) of *multiple event reporting* for the varenicline miscellaneous drug groups compared to the psychosis/mania or aggression drug groups (each about 20%). Multiple event reporting for bupropion was 26% which was slightly higher than the psychosis/mania (18%) and aggression (11%) groups.

For varenicline, the three most commonly reported events were anxiety and depression (both labeled as frequent) and feeling abnormal (not labeled) which were experienced collectively by a little more than half (260/380) of the patients. Two of the three most commonly reported events for bupropion were the same as for varenicline which include anxiety (labeled) and depression (labeled as *frequent*). The third most commonly reported event for bupropion was agitation (not labeled). Together these three events (anxiety, depression, agitation) were *collectively* reported in 60% of the bupropion patients. Like the other event groups there was a higher proportion of patients experiencing a significant change from the past with varenicline (29%) vs. bupropion (none). Most (82%) of these significant behavioral changes were disease worsening (anxiety was the most common).

Some of the reported miscellaneous events that were reported or coded were less specific than others. The least specific terms included *feeling abnormal*, *emotional disorder*, *abnormal behavior*, *personality change* and *thinking abnormal*. One-hundred-sixty varenicline and 10 bupropion cases had one or more of such. Examples of the literal descriptions of the events include (individual cases separated by semi-colon):

Varenicline: out of body experience, eyes twirling in head; in a bad fog, totally out of it; ready to be tied, Chantix made her go nuts; became woozy and felt strange; out of body experience

Bupropion: felt weird and was like being at two places at one time; out of control; speedy feeling, like amphetamine

Patient age was similar for both drug groups (median of approximately 49 years). Similar to the other two event groups (psychosis/mania and aggression), the patients were mostly female (75% varenicline; 60% bupropion).

An association between the miscellaneous event(s) and varenicline and bupropion was noted by a temporal relationship and positive dechallenge from the drugs. There was a short median time to onset of 3 and 6.5 days for each drug respectively and a positive dechallenge in more than one-half (55%) patients and about a third (32%) the bupropion patients. All of the varenicline and 30% of the bupropion cases reported a serious outcome. The two most frequent serious outcomes reported for varenicline were 'other' (86%) and hospitalization (21%); the same was found for bupropion ('other' and hospitalization both 15%). More patients recovered from their events with bupropion (62%) than with varenicline (29%); however, both drugs had unknown recovery reporting (35% and 40% respectively).

Between about one-quarter (24%) and a third (30%) of the varenicline and bupropion patients respectively had no prior reported psychiatric history. Varenicline had more patients with psychiatric history (42%) than bupropion (30%). However, there was more unknown reporting for this parameter for bupropion (50%) vs. varenicline (34%). The most commonly reported

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<sup>107</sup>Two events, n=80; three events, n=80; seven events, n=20.

psychiatric history for both drugs was depression (varenicline 18%; bupropion 8%), as seen with psychosis/mania and aggression.

Similar to the psychosis/mania group, there were a small proportion of patients that had no concomitant medications (varenicline 5%; bupropion 10%). For both drugs almost three-quarters of the patients had taken concomitant psychiatric medication(s) (73% varenicline; 70% bupropion). These proportions were higher than the psychosis/mania or the aggression groups. The most common psychiatric medications taken were benzodiazepines for varenicline and antidepressants for bupropion.

As in the psychosis/mania and aggression groups, smoking status at the time of the event(s) was mostly unknown (varenicline 87%; bupropion 83%). Where known, for varenicline (n=50)<sup>108</sup> patients, more patients had quit (n=30) vs. smoking (n=20). For bupropion (n=14), it was the reverse: less patients (n=6) had quit than were smoking (n=8). For the known non-smoking patients in the varenicline group (n=30), there was no mention of nicotine withdrawal in the reports. For bupropion, in 4/6 reports the reporter felt that bupropion had enhanced the nicotine withdrawal symptoms which were anxiety (n=2) and emotional disorder, agitation, and depression (n=2).

There was very little mention of alcohol (varenicline 5%; bupropion none) and the miscellaneous psychiatric events group mentioned it the least out of all the other event groups (psychosis/mania and aggression). For varenicline, when there was a mention, it was not for concomitant use but for past use.

#### 4.1.4 Overall

The sampling employed in this consult enabled a profile to be presented from the large miscellaneous population (for both drugs) using a workable hands-on sample in the range of 50 cases for each drug. This sampling allowed the remaining resources of the DPV-2 reviewer to review 100% of the reports for the psychosis/mania and aggression groups for both drugs. These latter two groups contained events such as hostility, aggression, psychosis, hallucination, mania and delusion which have been of concern to the FDA and the outside community since the media report of the Albrecht death in September, 2007.<sup>109,110</sup>

The case series in this consult of 625 reports (taking into account sampling) had a higher proportion of varenicline/bupropion (5/1) that was seen in the suicidality AERS case series (2/1).<sup>111</sup> However the time periods for the two reviews were different (this consult: first 417 days of marketing for both drugs; suicidality: entire period of marketing for both drugs). This larger proportion of varenicline vs. bupropion reports seen across all event groups in this review becomes even more significant as the first 417-days of varenicline marketing-time period was chosen to avoid the stimulated reporting period that commenced around September 2007. This preponderance of varenicline cases parallels the reporting rates which at least for psychosis/mania and aggression were higher for varenicline vs. bupropion. As with the

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<sup>108</sup> All these numbers mentioned for smoking-related parameters represent the population, not the sample.

<sup>109</sup> Eiserer, T. Autopsy: Carter Albrecht intoxicated 3 times the legal limit. *The Dallas Morning News* 10/22/07. <http://www.dallasnews.com/sharedcontent/dws/news/localnews/stories/102207dnmetalbrecht.197ab4f40.html>

<sup>110</sup> Early Communication About an Ongoing Safety Review: Varenicline (marketed as Chantix); 11/20/07; [http://www.fda.gov/cder/drug/early\\_comm/varenicline.htm](http://www.fda.gov/cder/drug/early_comm/varenicline.htm). See second section: **Aggressive and Erratic Behavior**.

<sup>111</sup> Pollock M, Lee J, Mosholder M, Governele L. OSE postmarketing review: Suicidality with smoking cessation drugs (varenicline, bupropion, nicotine transdermal patch); OSE RCM# 2007-2425.; 7/16/08

suicidality case series, bupropion did have cases of non-suicidal psychiatric events of similar quality as varenicline, although less of them.

There were other similarities between this case series ('this review') and what was found in the AERS suicidal case review. The gender was predominantly female (about 2/1) for the suicidal and non-suicidal psychiatric event reviews. Association of drugs and events were seen in both reviews as evidenced by a short onset to event time (one week non-suicidal; 2 weeks suicidal). In both reviews, on average there was at least 30% or more cases with positive dechallenges. Both reviews also had on average of at least one quarter of the patients having a psychiatric medical history and or exposure to concomitant psychiatric medications.

Both varenicline and Zyban labeling mention that nicotine withdrawal may be a confounding issue when a patient experiences psychiatric-related events while taking the respective drugs.<sup>112</sup> For varenicline there were a small number of patients (7%; 39/526) across all event groups that reported smoking when they experienced their event(s). For bupropion, smoking at the time of the event(s) was also reported for a small number of patients in the miscellaneous group (overall: 8/99; 8%). Even though the proportion of patients that were smoking at the time of the event(s) was small throughout this case series, this can be considered evidence that the event(s) not related to nicotine withdrawal. The reporting of *no-smoking* status was also low across all event groups for varenicline (48/526; 9%) and bupropion (7/99; 7%). Of these patients that were not smoking, the only ones where the reporter thought that nicotine withdrawal was enhanced was in a few bupropion patients who experienced miscellaneous events (see 4.1.3) Smoking status information in the suicidal AERS case series was also known only for a minority of cases: 25% and 15% for varenicline and bupropion respectively.

The use of alcohol with varenicline has been a concern ever since the Albrecht sentinel case in which in addition to his varenicline exposure, the celebrity musician was also intoxicated with alcohol when exhibiting the bizarre behavior, which resulted in his death.<sup>109</sup> However, similar to the AERS suicidal review, in this case series, there was very little mention (varenicline 8%; bupropion 9%) of the status of alcohol use in this case series of non-suicidal psychiatric events. There were four varenicline reports (psychosis/mania n=3; aggression, n=1) that did report *concomitant* alcohol use. One of the patients (aggression group) may have had a synergistic effect with alcohol and varenicline. The remaining three patients (psychosis/mania group), had taken other CNS-acting medications<sup>113</sup> in the addition to the alcohol which have contributed to an alcohol interaction. The limited information from this case series does allow assessment of the effect of alcohol on the psychiatric events. Patients with history of alcohol abuse were excluded from the varenicline clinical trials.<sup>114</sup> Additional information about the effects of alcohol may come from a thorough review of the sponsor's postmarketing adverse event database and or from new clinical trials where alcohol consumption is recorded from patients across a wide range of alcohol exposures (e.g. from moderate to abuse).

## 4.2 EPIDEMIOLOGY

The sponsor's analysis of varenicline clinical trial data showed some imbalances in the frequency of psychiatric events in certain categories, but overall the data were sparse and of limited inferential value. To place these data in context, it must be emphasized that patients with psychiatric disorders were largely excluded from the varenicline clinical trial program. Of more

<sup>112</sup>Zyban labeling specifically refers only to *depression* as the event associated with nicotine withdrawal.

<sup>113</sup>One of the following for each patient: benzodiazepine, antidepressant, and opioid

<sup>114</sup>Leeman RF, Huffman CJ, O'Malley S. Alcohol history and smoking cessation in nicotine replacement therapy, bupropion sustained release and varenicline trials: a review. *Alcohol and Alcoholism* 2007;42:196-206.

utility may be the data on adverse psychiatric events from the ongoing Department of Veterans' Affairs study among a post-traumatic stress disorder population although this trial has the weakness of not being randomized in design.

Disproportionality analyses of spontaneous reports show a higher than expected number of reports of the psychiatric events of interest with varenicline, but interpretation of such data must be made cautiously and causality can not be inferred from disproportional reporting in and of itself. Both drugs showed disproportionate reporting for a number of the MedDRA PT of interest, but the disproportion was frequently greater for varenicline compared to bupropion particularly with respect to violence, hostility, psychotic disorder including bipolar disorders, mania, and schizophrenia, stress, and emotional disorders. The disproportionality analyses cannot determine, however, whether the psychotic disorders are related to the treatment population affected (smoking cessation treatment in a population with pre-existing psychoses) or to the incidence or exacerbation of psychoses.

The reporting rates suggest a two- to three-fold increase in reports of psychosis and aggression for varenicline compared to bupropion during the first 14 months of marketing.

The literature review showed that although smoking prevalence has declined from 43.8% in 1965 to 20.9% in the general adult population in the United States in 2005<sup>115</sup>, smoking rates were found to be two- to four-fold higher among people with mental illness than in the general population<sup>116, 117, 118</sup>. Lasser and colleagues found that among current smokers in the U.S, 40.6% reported having a history of mental illness and those with a mental disorder consume nearly half of the cigarettes smoked in the US<sup>119</sup>. However, such smokers with serious psychiatric illness did not participate in the clinical trials of Chantix. Therefore, the safety and efficacy data among this subgroup of smokers cannot be determined. The results from the Chantix pre-marketing studies cannot be generalized to the whole smoker population.

The literature review did not find any consistent evidence supporting that smoking cessation alone may be associated with specific neuropsychiatric events. The conflicting results may be due to the limitation of study design or limited sample size.

However, this literature review observed that patients with a history of depression or major depressive disorder (MDD) had an increased risk of MDD after smoking cessation in most studies. Interestingly, the effects of smoking abstinence on patients with pre-existing neuropsychiatric conditions other than depression (e.g., schizophrenia or schizoaffective disorder) show no exacerbation or are inconclusive. Again, the limited sample size of those studies in patients with schizophrenia or schizoaffective disorder may lead to the insignificant findings.

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<sup>115</sup> Centers for Disease Control and Prevention. Cigarette smoking prevalence among adults. MMWR weekly. 2006; 55(10): 287

<sup>116</sup> Kalman D, Morissette SB, George TP. Co-morbidity of smoking in patients with psychiatric and substance use disorders. *Am J Addict.* 2005;14:106-123.

<sup>117</sup> Dalack GW, Healy DJ, Meador-Woodruff JH. Nicotine dependence and schizophrenia: Clinical phenomenon and laboratory findings. *Am J Psychiatry.* 1998;155:1490-1501.

<sup>118</sup> de Leon J, Diaz FH. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking. *Schizophr Res.* 2005;76:135-157.

<sup>119</sup> Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: A population-based prevalence study. *JAMA.* 2000;284:2606-2610.



## 5 CONCLUSION

### 5.1 AERS CASES

- The AERS case series for non-suicidal psychiatric events for the early (417 days) of varenicline marketing (pre-stimulated reporting) and a comparable period for bupropion consisted of 625 US reports. The case series was mostly varenicline (526/625; 84%) vs. bupropion (99/625; 16%).
- For both drugs, most (~80%) of the cases reported miscellaneous events.<sup>120</sup> Anxiety and depression were the two most commonly reported events for both drugs.
- For both drugs, ~20% of the cases reported psychosis/mania or aggression-events.<sup>120</sup> For varenicline, the most common event for the psychosis/mania and aggression groups was *hallucination* and *aggression* respectively; for bupropion it was *paranoia* and *hostility* respectively.
- There was a temporal association between the two drugs and all groups of events with a median onset time between 3 and 7 days. Positive dechallenge was reported in 33% and 63% of the varenicline and bupropion cases respectively.
- For all event groups, patients with no reported psychiatric history ranged from 17 to 33% for varenicline and 13 to 30% for bupropion.
- More varenicline patients (27%-53%) had a history of psychiatric disease than bupropion (0%-20%); however, there was a portion of the bupropion population for which unknown medical history was very high (78%). The most commonly reported psychiatric history across the case series was depression and bipolar disorder.
- For all event groups, patients with no reported concomitant psychiatric medications ranged from 4 % to 13% for varenicline and 0 to 25% for bupropion. Psychiatric medication use ranged from 13 to 73% for varenicline and 21% to 70% for bupropion. The most commonly reported drug classes for varenicline and bupropion was antidepressants for psychosis/mania and aggression and benzodiazepines for the miscellaneous groups.
- There were more cases of varenicline (29-33%) that reported a behavioral change from the patient's past (i.e., either new experience of disease worsening) than with bupropion (0-9%).
- Although only a minority of patients (varenicline 7%; bupropion 8%) reported smoking at the time of their event(s) this can be considered evidence that the psychiatric event(s) can occur independently of nicotine withdrawal.
- There were a few varenicline patients (psychosis mania, n=3; aggression, n=1) that had concomitant alcohol use and appeared to experience an interaction between varenicline and alcohol. The limited mention (varenicline 8%; bupropion 9%) of alcohol status for both drugs did not allow assessment of the effect of alcohol on the psychiatric events. Additional information about the effects of alcohol may come from a thorough review of

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<sup>120</sup>Because the reports with miscellaneous events were such a large proportion of the population, only a sample was hands on reviewed. All of the reports with psychosis/mania and aggression-events were hands on reviewed.

the sponsor's postmarketing adverse event database and or from new clinical trials where alcohol-related medical history is not excluded and alcohol consumption is recorded.

## 5.2 EPIDEMIOLOGY

- Two out of 3 RCTs and 4 out of 5 observational studies reviewed in the literature suggested that patients with a history of depression or major depressive disorder (MDD) had an increased risk of MDD after smoking cessation;
- Smoking cessation studies reported in the literature suggest an association and/or exacerbation between smoking cessation and depression, but are limited by design issues.
- New onset of MDD episodes can occur without history of depression;
- The effects of smoking abstinence per se on patients with pre-existing neuropsychiatric conditions other than depression (e.g., schizophrenia or schizoaffective disorder) show no exacerbation or are inconclusive;
- Smoking cessation with varenicline is associated with a higher incidence of other psychiatric symptoms (disturbed sleep, vivid dreams, anxiety, panic) compared to NRT.
- Clinical trial data for varenicline is sparse for the purpose of assessing the association between varenicline and these psychiatric events. Patients with psychiatric disorders were excluded from varenicline clinical trials.
- Smoking cessation studies reported in the literature suggest an association and/or exacerbation between smoking cessation and depression, but are limited by design issues.
- The spontaneous reporting rates for psychosis and aggression events were higher for varenicline compared to Zyban during the first 14 months of marketing, even before the publicity about such events with Chantix.
- Data mining shows a disproportionate reporting for a number of psychiatric events of interest, more prominent for varenicline than for Zyban particularly with respect to violence, hostility, psychotic disorder including bipolar disorders, mania, and schizophrenia, stress, and emotional disorders.
- Preliminary data from a Veterans' Affairs study suggests a higher rate of psychiatric adverse events with varenicline use compared to other smoking cessation therapies, but these treatments were not randomly assigned.

## 6 RECOMMENDATIONS

### 6.1 Varenicline

#### 6.1.1 Epidemiologic-related studies

Efforts should continue to be made to obtain more data from the VA study CSP-519.

#### 6.1.2 Labeling

Portions of the varenicline labeling that are underlined are changes that were recommended from the OSE review of suicidality-related events.<sup>121</sup> In the suicidality consult, OSE has also recommended that the current **WARNINGS: Neuropsychiatric Symptoms** be elevated to a **Box Warning**.

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<sup>121</sup>Pollock M, Lee J, Mosholder M, Governele L. OSE postmarketing review: Suicidality with smoking cessation drugs (varenicline, bupropion, nicotine transdermal patch); OSE RCM# 2007-2425; 7/16/08.

Labeling mentioned in *italics*, below are additional recommendations to be put into the proposed Box Warning for non-suicidal psychiatric events. Such additional events have been considered only if they have been reported in this AERS case series two or more times.

## **BOX WARNING:**

### **Neuropsychiatric Symptoms**

Serious neuropsychiatric symptoms have occurred in patients being treated with CHANTIX. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking; however, some of these symptoms have occurred in patients who continued to smoke. In most cases, neuropsychiatric symptoms developed during Chantix treatment, but in others, symptoms developed following withdrawal of Chantix therapy. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including agitation *anger*, changes in behavior, *delusion*, depressed mood, hallucination, *homicidal ideation*, *mania*, *paranoia*, *psychosis*, suicidal ideation and completed suicide. These symptoms, as well as worsening of pre-existing psychiatric illnesses and experiences *such as anger, anxiety, bipolar disorder, depression, hallucinations, mania, panic disorders psychosis, and schizophrenia* have been reported in patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established. Patients attempting to quit smoking with CHANTIX and their families and caregivers should be alerted about the need to monitor for these symptoms and to report such symptoms immediately to the patient's healthcare provider.

## **ADVERSE REACTIONS**

### **Post Marketing Experience:**

There have been reports of *aggression*, agitation *anger*, changes in behavior, *delusion*, depressed mood, hallucination, *homicidal ideation*, *mania*, *paranoia*, *psychosis*, suicidal ideation and completed suicide in patients attempting to quit smoking while taking Chantix. In most cases, neuropsychiatric symptoms developed during Chantix treatment, but in others, symptoms developed following withdrawal of Chantix therapy. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. The role of Chantix in these reports is not known (see **WARNINGS**).

## **6.2 BUPROPION (ZYBAN)**

### **BOX WARNING AND PRECAUTIONS**

***Depression and Nicotine Withdrawal:*** Depressed mood may be a symptom of nicotine withdrawal. Depression,<sup>122</sup> including suicidal ideation, has been reported in patients undergoing a smoking cessation attempt. (see **WARNINGS: Clinical Worsening and Suicide Risk**). *Enhanced nicotine withdrawal symptoms of anxiety, aggression, and emotional disorder have been reported in patients taking Zyban for smoking cessation.*

## **ADVERSE REACTIONS**

### **Other Events Observed During the Clinical Development and Postmarketing**

**Experience of Bupropion:** In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the

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<sup>122</sup> Current Zyban labelling states: Depression, *rarely* including suicidal ideation.....OSE recommends deleting 'rarely.'

sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion:

**Nervous System:**<sup>123</sup> Frequent were agitation, depression, and irritability. Infrequent were abnormal coordination, CNS stimulation, confusion, decreased memory, depersonalization, emotional lability, hostility, suicidal ideation, and. Rare were amnesia, derealization, and hypomania. Also observed were aggression, *anger*, delirium, delusions, *disorientation*, *emotional disorder*, euphoria, *feeling abnormal*, hallucinations, manic reaction, *mood altered*, *mood swings*, paranoid ideation, *psychotic disorder*, restlessness.

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<sup>123</sup>Nervous system terms that are listed in the labeling, but were not included as search criteria for this review, have been deleted in this presentation. These nervous system terms will remain in the labeling.

## 7 APPENDICES

### APPENDIX 1. PRODUCT LABELLING FOR VARENICLINE AND BUPROPION

#### 1.1 VARENICLINE

##### WARNINGS

###### Neuropsychiatric Symptoms

Serious neuropsychiatric symptoms have occurred in patients being treated with CHANTIX. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking; however, some of these symptoms have occurred in patients who continued to smoke. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, suicidal ideation and suicidal behavior. These symptoms, as well as worsening of pre-existing psychiatric illness, have been reported in patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients have not been established. Patients attempting to quit smoking with CHANTIX and their families and caregivers should be alerted about the need to monitor for these symptoms and to report such symptoms immediately to the patient's healthcare provider.

##### ADVERSE REACTIONS

###### Clinical Trials

Insomnia, abnormal dreams, sleep disorder, nightmare<sup>124</sup>

###### Other events

**Nervous System Disorders.**<sup>125</sup> **Frequent:** Disturbance in attention, **Infrequent:** Amnesia, Parosmia, Psychomotor hyperactivity. **Rare:** Balance disorder, Mental impairment, Psychomotor skills impaired.

**Psychiatric Disorders.** **Frequent:** Anxiety, Depression, Emotional disorder, Irritability, Restlessness. **Infrequent:** Aggression, Agitation, Disorientation, Dissociation, Libido decreased, Mood swings, Thinking abnormal. **Rare:** Bradyphrenia, Euphoric mood, Hallucination, Psychotic disorder, Suicidal ideation.

###### Post Marketing

There have been reports of depressed mood, agitation, changes in behavior, suicidal ideation and suicide in patients attempting to quit smoking while taking Chantix. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. The role of Chantix in these reports is not known (see **WARNINGS**).

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<sup>124</sup>  $\geq 1\%$  with varenicline or difference between varenicline and placebo  $\geq 0.5\%$ .

<sup>125</sup> Nervous system terms that are listed in the labeling, but were not included as search criteria for this review have been deleted.

## 1.2 BUPROPION (ZYBAN)

### SUICIDALITY AND ANTIDEPRESSANT DRUGS (BOX WARNING)

Although ZYBAN is not indicated for treatment of depression, it contains the same active ingredient as the antidepressant medications WELLBUTRIN®, WELLBUTRIN SR®, and WELLBUTRIN XL®. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of ZYBAN or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ZYBAN is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

### WARNINGS

**All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.**

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

**Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for ZYBAN should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

**Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately

screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that ZYBAN is not approved for use in treating bipolar depression.

## PRECAUTIONS

**Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

**Psychosis, Confusion, and Other Neuropsychiatric Phenomena:** In clinical trials with ZYBAN conducted in nondepressed smokers, the incidence of neuropsychiatric side effects was generally comparable to placebo. Depressed patients treated with bupropion in depression trials have been reported to show a variety of neuropsychiatric signs and symptoms including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

**Activation of Psychosis and/or Mania:** Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible individuals. The sustained-release formulation of bupropion is expected to pose similar risks. There were no reports of activation of psychosis or mania in clinical trials with ZYBAN conducted in nondepressed smokers

**Depression and Nicotine Withdrawal:** Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in patients undergoing a smoking cessation attempt (see **WARNINGS: Clinical Worsening and Suicide Risk**).

## ADVERSE REACTIONS

### Clinical Trials

Insomnia, dream abnormality, anxiety, disturbed concentration, nervousness, dysphoria, thinking abnormality<sup>126</sup>

### Other Events from clinical trials and postmarketing

**Nervous System.**<sup>127</sup> Frequent were agitation, depression, and irritability. Infrequent were abnormal coordination, CNS stimulation, confusion, decreased memory, depersonalization, emotional lability, hostility, suicidal ideation, and. Rare were amnesia, derealization, and hypomania. Also observed were aggression, delirium, delusions, euphoria, hallucinations, manic reaction, paranoid ideation, restlessness.

<sup>126</sup> ≥1% with Zyban or more frequent than placebo.

<sup>127</sup> Nervous system terms that are listed in the labeling, but were not included as search criteria for this review have been deleted.

**APPENDIX 2. COMPARISONS OF SELECTED PARAMETERS FOR FULL AND SAMPLED POPULATIONS FOR MISCELLANEOUS EVENTS FOR VARENICLINE AND BUPROPION**

<b>VARENICLINE</b>				
<b>Parameter</b>	<b>Entire population (n=461)</b>		<b>Sampled population (n=47)</b>	
		Percent		Percent
Gender				
Male	119	25.8	13	27.7
Female	333	72.2	34	72.3
Unknown	9	2.0	0	0.0
Age (evaluable)	393	85.2	42	89.4
Mean (years)	51.2		53.0	
Median (years)	51		52.5	
Range (years)	18 to 84		31 to 83	
Report type				
Periodic	1	0.2	0	0.0
Direct	39	8.5	6	12.8
Expedited	421	91.3	41	87.2
FDA received date (quarters)				
>=7/10/06 and <=10/9/06	11	2.4	1	2.1
>=10/10/06 and <=1/09/07	57	12.4	9	19.1
>=1/10/07 and <=4/9/07	113	24.5	7	14.9
>=4/10/07 and <=7/9/07	154	33.4	14	29.8
>=7/10/07 and <=8/31/07	126	27.3	16	34.0
Reporter				
Evaluable	437	94.7	45	95.7
Consumer	281	64.3	25	55.6
HCP	113	25.9	12	26.7
Other	43	9.9	8	17.8



VARENICLINE				
Parameter	Entire population (n=461)		Sampled population (n=47)	
Outcome [first only]				
Non serious'	5	1.1	0	0.0
Serious	456	98.9	47	100.00
Death	1	0.2	0	0.0
Hospitalized	39	8.5	7	14.9
Disability	14	3.0	0	0.0
Life-threatening	5	1.1	1	2.1
Other	397	86.1	39	83.0
Event date (evaluable)	414	89.8	44	93.6%
>=1 other medication(s) <sup>128</sup>	360	78.1%	38	80.8
Preferred terms (selected)				
Anxiety	105	22.8	12	25.5
Insomnia	52	11.3	8	17.0
Agitation	34	7.4	3	6.4
Depression	106	23.0	9	19.1
Nervousness	59	12.8	4	8.5
Confusional state	37	8.0	4	8.5
Dizziness	50	10.8	5	10.6
Thinking abnormal	17	3.7	1	2.1

<sup>128</sup>Suspect and or concomitant

BUPROPION				
Parameter	Entire population (n=115)		Sampled population (n=58)	
		Percent		Percent
Gender				
Male	38	33.0	20	34.5
Female	76	66.1	38	65.5
Unknown	1	0.9	0	0.0
Age (evaluable)	101	87.8	56	96.6
Mean	49.4		48.9	
Median	50		48.5	
Range	26 to 75		26 to 70	
Report type				
Periodic	95	82.6	45	77.6
Direct	5	4.3	0	0.0
Expedited	15	13.0	13	22.4
FDA received date (quarters)				
5/14/07-8/31/07	2	1.7	0	0.0
9/1/07 and <=12/31/07	58	50.4	29	50.0
>=1/1/98 and <=4/30/98	14	12.2	8	13.8
>=5/1/98 and <=7/5/98	41	35.7	21	36.2
Reporter				
Evaluable	110	95.7	58	100.0
Consumer	83	72.2	46	79.3
HCP	27	23.5	12	20.7
Outcome [first only]				
Non serious	71	61.7	35	60.3
Serious	44	38.3	23	39.7

BUPROPION				
Parameter	Entire population (n=115)		Sampled population (n=58)	
Death	0	0.0	0	0.0
Hospitalized	19	16.5	11	19.0
Other	16	13.9	7	12.1
Event date (evaluatable)	64	55.7	38	65.5
>=1 other medication(s) <sup>129</sup>	76	66.1	41	70.7
Preferred terms (selected)				
Anxiety	26	22.6	11	19.0
Insomnia	25	21.7	12	20.7
Agitation	25	21.7	12	20.7
Depression	22	19.1	10	17.2
Nervousness	20	17.4	8	13.8
Confusional state	15	13.0	7	12.1
Dizziness	15	13.0	6	10.3
Thinking abnormal	7	6.1	6	10.3

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<sup>129</sup>Suspect and or concomitant

**APPENDIX 3. OTHER CO-REPORTED PSYCHIATRIC-RELATED EVENTS  
FOR PSYCHOSIS/MANIA-RELATED EVENTS**

Varenciline (N=74)			Bupropion (N=9)		
Rank	Event	n	Rank	Event	n
1	abnormal dreams	17	1	insomnia	4
2	insomnia	15	2	disorientation	3
3	anxiety	13	3	anxiety	3
4	feeling abnormal	12	4	nervousness	2
5	irritability	8	5	tremor	1
	confusional state	7	5	psychomotor hyperactivity	1
	hypersomnia	7	5	panic attack	1
	depression	7	5	memory impairment	1
	tremor	6	5	hostility	1
	panic attack	6	5	emotional distress	1
	agitation	6	5	emotional disorder	1
	amnesia	6	5	depression	1
	nervousness	6	5	crying	1
	memory impairment	6	5	agitation	1
	mood swings	5	5	post-traumatic stress disorder (worsened)	1
	suicidal ideation	5			
	abnormal behaviour	4			
	thinking abnormal	4			
	crying	3			
	emotional disorder	3			
	nightmare	3			
	disturbance in attention	3			
	fear	3			
	mania	3			
	somnolence	3			
	sleep disorder	2			
	drug dependence	2			
	loss of consciousness	2			
	convulsion	2			
	disorientation	2			
	restlessness	2			
	mental status changes	2			
	poor quality sleep	2			
	personality change	2			
	depressed mood (n=1)	1			
	aggression	1			
	anger	1			
	anorexia	1			
	bedridden	1			
	bipolar disorder	1			
	conversion disorder	1			
	dissociation	1			
	drug withdrawal syndrome	1			
	eating disorder	1			
	emotional distress	1			
	food craving	1			
	hostility	1			
	hypoacusis	1			
	impaired work ability	1			
	major depression	1			

Varenciline (N=74)			Bupropion (N=9)		
Rank	Event	n	Rank	Event	n
	narcolepsy	1			
	negative thoughts	1			
	panic disorder	1			
	parosmia	1			
	post-traumatic stress disorder	1			
	psychomotor hyperactivity	1			
	psychotic disorder	1			
	schizophrenia, paranoid type	1			
	screaming	1			
	serotonin syndrome	1			
	sleep talking	1			
	social avoidant behaviour	1			
	social phobia	1			
	somnambulism	1			
	stress	1			
	suicide attempt	1			
	tobacco withdrawal symptoms	1			

**APPENDIX 4. OTHER CO-REPORTED PSYCHIATRIC-RELATED EVENTS  
FOR AGGRESSION-RELATED EVENTS**

Varenciline (N=43)			Bupropion (N=8)		
Rank	Event	n	Rank	Event	n
1	insomnia	8	1	insomnia	3
2	anxiety	8	2	mood swings	2
3	abnormal dreams	7	3	irritability	2
4	depression	7	4	depression	3
5	irritability	7	5	tobacco withdrawal symptoms	1
	agitation	6	5	suicidal ideation	1
	nightmare	5	5	nervousness	1
	crying	5	5	emotional distress	1
	emotional disorder	4	5	emotional disorder	1
	feeling abnormal	4	5	disturbance in attention	1
	mood altered	3	5	dissociation	1
	disturbance in attention	3	5	disorientation	1
	stress	3	5	crying	1
	abnormal behaviour	3	5	agitation	1
	suicidal ideation	3			
	memory impairment	3			
	mental disorder	3			
	impaired work ability	3			
	mood swings	3			
	amnesia	3			
	somnolence	3			
	screaming	3			
	hypersomnia	2			
	psychomotor hyperactivity	2			
	nervousness	2			
	loss of consciousness	2			
	mania	2			
	cognitive disorder	2			
	confusional state	2			
	disorientation	1			
	anorexia	1			
	tearfulness	1			
	suicide attempt	1			
	communication disorder	1			
	drug dependence	1			
	depressed mood	1			
	drug interaction	1			
	drug withdrawal syndrome	1			
	tobacco withdrawal symptoms	1			
	expressive language disorder	1			
	dissociation	1			
	narcolepsy	1			
	speech disorder	1			
	sleep disorder	1			
	psychotic disorder	1			
	personality change	1			
	panic attack	1			
	overdose	1			
	obsessive compulsive disorder	1			
	impaired driving ability	1			
	nervous system disorder	1			
	formication	1			

Varenciline (N=43)			Bupropion (N=8)		
Rank	Event	n	Rank	Event	n
	mental status changes	1			
	loss of employment	1			
	tremor	1			
	impatience	1			
	lethargy	1			
	hallucination, tactile	1			
	hallucination	1			
	nicotine dependence	1			

**APPENDIX 5. OTHER CO-REPORTED PSYCHIATRIC-RELATED EVENTS  
FOR MISCELLANEOUS-RELATED EVENTS**

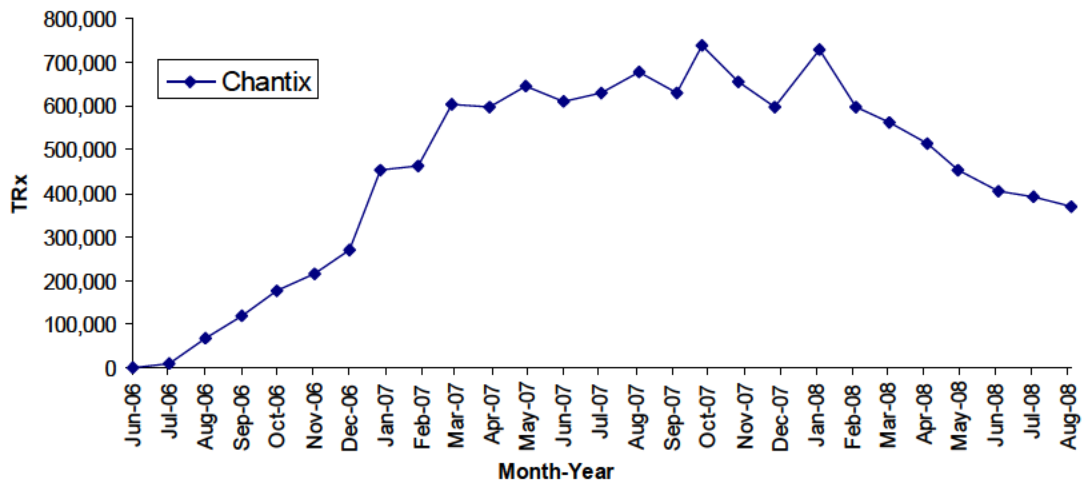
Varenciline (N=24)			Bupropion (N=26)		
Rank	Event	n	Rank	Event	n
1	insomnia	n	1	insomnia	10
2	irritability	7	2	disturbance in attention	4
3	nightmare	5	3	irritability	4
4	mental disorder	4	4	crying	4
5	paranoia	4	5	psychomotor hyperactivity	3
	suicidal ideation	3		paranoia	2
	euphoric mood	2		nicotine dependence	2
	drug withdrawal syndrome	2		tobacco withdrawal symptoms	2
	mania	2		apathy	1
	disturbance in attention	2		communication disorder	1
	hallucination	2		conversion disorder	1
	anger	2		depersonalisation	1
	abnormal dreams	2		aggression	1
	crying	2		mental impairment	1
	screaming	2		psychotic disorder	1
	aggression	2		suicidal ideation	1
	apathy	1			
	flat affect	1			
	food craving	1			
	drug dependence	1			
	formication	1			
	tremor	1			
	suicide attempt	1			
	violence-related symptom	1			
	mental impairment	1			
	premenstrual syndrome	1			
	psychomotor hyperactivity	1			
	psychotic disorder	1			
	restlessness	1			
	social avoidant behaviour	1			
	hypersomnia	1			



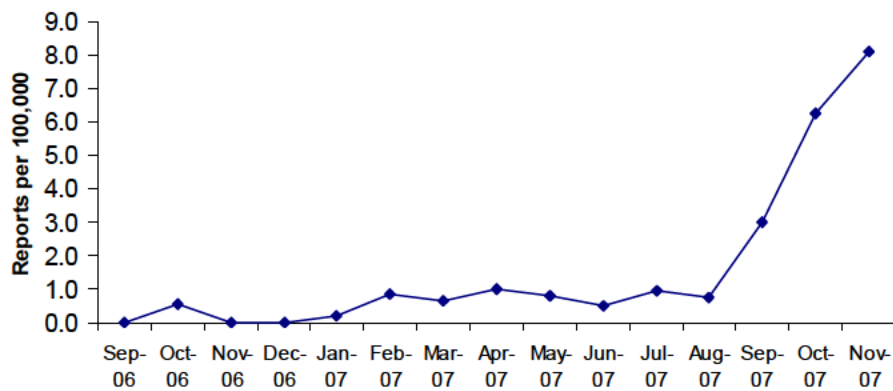
## APPENDIX 6. TOTAL RETAIL PRESCRIPTIONS OF CHANTIX AND REPORTS OF SUICIDE IDEATION AND HARM PER TOTAL PRESCRIPTIONS

**Total number of prescriptions dispensed for Chantix from outpatient retail pharmacies in the U.S., Jun 2006 - Aug 2008**

SDI Vector One®: National, Extracted Oct-08



**Report of Suicide Ideation and Harm per Total Prescriptions by Month - Chantix**



\*Source: SDI: Vector One®: National (VONA; by month: Chantix for 2008).

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/s/

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Martin Pollock  
12/8/2008 05:31:17 PM  
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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology Review (OSE)  
Office of Pharmacovigilance and Epidemiology (OPE)**

**Epidemiology: Review of labeling supplement regarding neuropsychiatric events  
associated with varenicline**

Date:	September 12 <sup>th</sup> 2014
Reviewer(s):	Chih-Ying Chen, Ph.D. Division of Epidemiology II
Team Leader	Elizabeth M. Maloney, M.S., Dr.P.H. Division of Epidemiology II
Division Director	Judy A. Staffa, Ph.D., R.Ph Division of Epidemiology II
Drug Name(s):	Varenicline (Chantix)
Subject:	Labeling supplement regarding neuropsychiatric events associated with varenicline
Application Type/Number:	NDA 21-928
Submission Number:	036
Applicant/sponsor:	Pfizer
OSE RCM #:	2014-749

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## EXECUTIVE SUMMARY

Varenicline was approved under the trade name of Chantix as an aid to smoking cessation treatment for adults in May 2006. In February 2009, FDA requested that the sponsor add to the varenicline label additional warnings and precautions regarding neuropsychiatric events including, but not limited to, depression, suicidal ideation and behavior, which had been reported during post approval use of varenicline. Due to the potential seriousness of these events, FDA requested the addition of a boxed warning based on the accrual of postmarketing reports of neuropsychiatric events since approval of the drug.

In April 2014, the sponsor submitted a labeling supplement including meta-analyses of clinical data for varenicline, a literature review of observational and clinical studies, and proposed labeling revisions. The sponsor proposed revisions to the Warnings and Precautions section of the package insert (PI) regarding the risk of neuropsychiatric events with varenicline and removal of the boxed warning. The Division of Anesthesia, Analgesia and Addictive Products (DAAAP) consulted the Division of Epidemiology II (DEPI II) to review the observational studies submitted by the sponsor and to determine if they support modification of the current warning on neuropsychiatric adverse events (AE).

The sponsor identified five observational studies on varenicline's neuropsychiatric risk (four publications and one unpublished study), including three which examined the association between varenicline and risk of neuropsychiatric hospitalizations, and two which investigated the association between varenicline and risk of suicide, non-fatal self-harm and initiation of an antidepressant. All the reviewed observational studies used population-level data reflecting the real-world smoking cessation drug user population. Their inclusion of patients with neuropsychiatric history extends the generalizability of the findings, because that population was excluded in most clinical trials conducted to date. The studies also all attempted to control for confounding by employing appropriate design and analytical approaches. Nonetheless, due to the due to 1) concerns about the examined outcomes and outcome measure validity, 2) using bupropion (another smoking cessation drug with risk of neuropsychiatric events) as a reference, 3) channeling bias and residual confounding between varenicline users and nicotine replacement therapy (NRT) users, and 4) limited statistical power, evidence from the observational studies reviewed is of insufficient quality to either rule in or rule out an increased risk of suicide, non-fatal self-harm, or neuropsychiatric hospitalizations associated with varenicline use. While these studies appear reassuring, they do not adequately measure the effect of Chantix on the risk of neuropsychiatric adverse events of concern and therefore cannot be interpreted to mean that there is no increased risk of neuropsychiatric events with Chantix.

DEPI II does not recommend including the findings of the five observational studies as currently proposed in the label revision, due to the limitations of those studies that were addressed in this review. We also are not inclined to remove the boxed warning at this time because of the concern that such action could be interpreted as confirming "no association" between varenicline use and neuropsychiatric risk, which is not supported by currently available observational data. Given that the sponsor is conducting a Phase IV trial to examine varenicline's neuropsychiatric safety, it might be more reasonable to discuss the decision on the boxed warning after the completion of the trial (the target completion date is August 2016), when further information regarding varenicline's neuropsychiatric risk is available. Alternatively, DEPI-II can suggest language for including observational studies in the boxed warning which includes the appropriate interpretation of the studies' findings.

## 1 INTRODUCTION

Varenicline was approved under the trade name of Chantix as an aid to smoking cessation treatment for adults in May 2006. In February 2009, FDA requested that the sponsor add to the varenicline label additional warnings and precautions regarding neuropsychiatric events including, but not limited to, depression, suicidal ideation and behavior, which had been reported during post approval use of varenicline. Due to the potential seriousness of these events, FDA requested the addition of a boxed warning based on the accrual of postmarketing reports of neuropsychiatric events since approval of the drug.

In April 2014, the sponsor submitted a labeling supplement with data from clinical and observational studies for varenicline and proposed revisions to the Warnings and Precautions section of the PI regarding the risk of neuropsychiatric events with varenicline and removal of the boxed warning. The Division of Anesthesia, Analgesia and Addictive Products (DAAAP) consulted the Division of Epidemiology II (DEPI II) to review the observational studies submitted by the sponsor and determine if they support modification of the current warning on neuropsychiatric adverse events (AE).

## 2 REVIEW MATERIALS

- Sponsor's clinical overview
- The proposed labeling changes
- Five observational studies on varenicline's neuropsychiatric risk cited in the clinical overview

## 3 REVIEW RESULTS

The sponsor identified five observational studies on varenicline's neuropsychiatric risk (four publications<sup>1-4</sup> and one unpublished study<sup>5</sup>). The design, data sources, methods, and main findings of each study are summarized in Appendix Table 1, Appendix Table 2 and Appendix Figure 1. The five reviewed studies include three which examined the association between varenicline and risk of neuropsychiatric hospitalizations<sup>2,3,5</sup> (see Section 3.1), and two which investigated the association between varenicline and risk of suicide, non-fatal self-harm and initiation of an antidepressant<sup>1,4</sup> (see Section 3.2).

### 3.1 VARENICLINE AND NEUROPSYCHIATRIC HOSPITALIZATIONS

All three studies that examined the association between varenicline and neuropsychiatric hospitalizations are retrospective cohort studies. Two of the three studies were sponsored by FDA; one was conducted by the Department of Veterans Affairs' (VA) Center for Medication Safety (unpublished)<sup>5</sup>, and the other by the Department of Defense's U.S. Army Medical Command's Pharmacovigilance Center, described in the publication by Meyer et al.<sup>2</sup>. The third study was sponsored by the Danish Medical Research Council, described in the publication by Pasternak et al.<sup>3</sup>.

The VA study<sup>5</sup> evaluated the incidence of neuropsychiatric hospitalizations among veterans using varenicline or nicotine replacement therapy (NRT). Patients starting varenicline or NRT between May 1, 2006 and September 30, 2007, but with no varenicline or NRT use in the previous year, were selected and matched in a 1:1 ratio by use of propensity scores (reflecting demographic characteristics, comorbidities, and psychiatric history). The study's main outcome was 30-day risk of psychiatric hospitalization, with a coded primary discharge diagnosis for one of a number of psychiatric conditions (Appendix Table 1). The study population included 14,131 varenicline users and an equal number of NRT users. Among these patients, there were 16 psychiatric hospitalizations in varenicline-treated patients, and 21 in NRT patients. No statistically significant difference was found in the 30-day risk of neuropsychiatric hospitalization for Varenicline users compared to NRT users (hazard ratio [HR] for varenicline/NRT = 0.76; 95% confidence interval [CI] 0.40-1.46). The trend was the same in the analyses using time periods longer than 30 days after a prescription fill. Similar findings were reported in a prevalent user cohort of patients who had used NRT in the past before initiating varenicline or refilling an NRT prescription.

The study by Meyer et al.<sup>2</sup> compared the rates of hospitalizations for neuropsychiatric adverse events among new users of varenicline and the NRT patch who started therapy between August 1, 2006 and August 31, 2007 in the Military Health System. Varenicline users were matched using propensity scores to NRT users, with subgrouping by concomitant use of the prescription smoking cessation drug bupropion, or a history of neuropsychiatric disease. After propensity score matching, there were 11,978 varenicline users and an equal number of NRT users in the study sample. The main outcome was a primary hospital discharge diagnosis for one of a number of neuropsychiatric condition (Appendix Table 1) within 30 days of drug initiation. In the study's propensity score matched samples, there were 16 psychiatric hospitalizations among varenicline users and 14 among NRT users. No statistically significant difference was found with respect to the risk of neuropsychiatric hospitalization comparing varenicline users to NRT users (HR 1.14; 95% CI 0.56-2.34). HRs were reduced further among patients without exposure to concomitant bupropion (HR = 0.70; 95% CI 0.27-1.84) or a history of neuropsychiatric disease (HR = 0.80; 95% CI 0.21-2.98). The trend was the same when patients were followed 60 days after drug initiation. Finding was similar when using any inpatient diagnosis as the outcome measure (HR 0.79, 0.50-1.24). The HR estimate was within the range reported for the main outcome, but indicating a lowered risk of outpatient neuropsychiatric visits (HR 0.71, 0.60-0.84) for varenicline users compared to NRT users.

The study by Pasternak et al.<sup>3</sup> compared the rates of emergency department visit or hospital admission with one of a number of psychiatric diagnoses (Appendix Table 1) that had occurred within 30 days of treatment initiation among new users of varenicline and bupropion who started therapy between January 1<sup>st</sup> 2007 and December 31 2010 in Denmark. Overall, 59,790 new users of varenicline and 17,936 new users of bupropion were identified. In this unmatched cohort, the distribution of baseline characteristics was generally similar between the two groups. To further control for confounders, 17,935 varenicline users were matched 1:1 to bupropion users. A total of 85 psychiatric events occurred. There were 39 (0.22%) psychiatric adverse events among 17,935 varenicline users (rate 27 events per 1000 person-years) and 46 (0.26%) events among 17,935 bupropion users (rate 31 per 1000). There were three cases of suicide attempt or completed suicide among varenicline users and one case among bupropion users. There was no significant association between varenicline use and psychiatric adverse events compared with bupropion use (HR: 0.85, 95% CI: 0.55- 1.30; Table 2). The risk of psychiatric events associated with varenicline compared with bupropion appeared lower in participants without a history of psychiatric disorder than in participants with a history, although this was based on few cases, and the difference in risk of psychiatric events associated with varenicline versus bupropion by history of psychiatric disorder was not statistically significant (P=0.12).

### 3.2 VARENICLINE AND SUICIDE RELATED OUTCOMES

The two studies that examined varenicline and suicide related outcomes (Gunnell et al. and Thomas et al.) were both conducted by researchers at the University of Bristol and were based on the same data source (the General Practice Research Database [GPRD], subsequently known as the Clinical Practice Research Datalink [CPRD]), per a grant received from the Medicines and Healthcare products Regulatory Agency (MHRA).<sup>1,4</sup>

The earlier study by Gunnell et al.<sup>1</sup> examined the 3-month risk of suicide, non-fatal self-harm and the initiation of antidepressants in 10,973 varenicline users, 6,422 bupropion users and 63,265 NRT users who received a prescription between September 01 2006 and May 31 2008. In multivariate analyses, no association was found for varenicline versus NRT with respect to self-harm (HR: 1.12, 95% CI: 0.67-1.88) or the initiation of antidepressants (HR: 0.88, 95% CI: 0.77-1.00). Two suicides were identified both within the NRT group, from the death details and postmortem findings recoded on GPRD. It should be noted that a previous study using the GPRD to determine the incidence of suicide among asthma patients yielded a rate below that of the general population, suggesting under-ascertainment of suicide.<sup>6</sup>

Thomas et al.<sup>4</sup> examined the 3-month risk of suicide-related outcomes and all-cause mortality in 31,260 varenicline users, 6,741 bupropion users and 81,545 NRT users who received their first prescription between September 01 2006 and October 31 2011. Ninety-two cases of suicide and non-fatal self-harm were identified from the linked UK CPRD, Office for National Statistics (ONS) mortality data and Health Episode Statistics (HES) data during 3 months of follow-up after the date of treatment initiation: 69 among NRT users, 4 among bupropion users and 19 among varenicline users. Comparing varenicline users to NRT users, the multivariate-adjusted HR for fatal and non-fatal self-harm included the null (HR=0.88, 0.52 to 1.49), but showed a lower risk of initiation of antidepressants (HR= 0.75, 0.65 to 0.87) and all-cause mortality (0.44, 0.30-0.63). Similar findings were reported using propensity score methods, but the direction of risk estimate changed in the instrumental variable analyses (See section 4.2 for further discussions). The trend did not change in most of the sensitivity analyses that extended the follow-up to 6-, or 9-months, as well as restricting to first-time users of smoking cessation drugs.

## 4 DISCUSSION

The five observational studies all used population-level data reflecting the real-world smoking cessation drug user population. The inclusion of patients with neuropsychiatric history extends the generalizability of the findings, because that population was excluded in most clinical trials conducted to date. They also all attempted to control for confounding by employing appropriate design and analytical approaches. Nonetheless, these studies themselves were not able to provide conclusive evidence with regard to the risk of neuropsychiatric adverse events associated with varenicline. We will address the specific limitations of the existing observational studies in the following sections.

### 4.1 CONCERNS REGARDING THE EXAMINED OUTCOMES AND VALIDITY OF OUTCOME MEASURES

The outcomes of interest in the existing studies—suicide, self-harm, neuropsychiatric hospitalizations, and initiation of antidepressants (used as a proxy for incident depression), although clinically meaningful, only capture some of the neuropsychiatric adverse events<sup>1</sup> that have been reported in association with varenicline use to FDA's adverse event reporting system. Moreover, all reviewed studies relied on diagnostic codes (ICD-9, ICD-10 or Read codes, etc.) to ascertain outcomes. We are concerned that diagnostic codes cannot accurately capture all the serious neuropsychiatric adverse events that have been associated with varenicline. Such events involve abrupt behavioral and/or mood changes, which are difficult to accurately translate into a medical coding system, and may result in patient contact with legal, rather than medical, systems. Without a detailed exploration of medical charts to identify all the codes that might be used to capture these outcomes, as well as patient and provider interviews to determine behavior and coding practices, it is not possible to estimate how many events were missed in those studies. Such problems are inherent to the study of behavioral and psychiatric outcomes, which present different challenges than studying purely medical events.

Additionally, it is difficult to interpret the findings on the outcomes that were captured. First, none of the reviewed studies reported the validity of the chosen codes. Only one study<sup>3</sup> reported some measure of validity for some of the ICD-10 codes used to identify their outcomes<sup>2</sup>. In the studies that examined the

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<sup>a</sup> There have been post marketing reports of neuropsychiatric symptoms, some serious, including changes in mood, agitation, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, changes in behavior, anxiety, panic, suicidal ideation, suicide attempt and completed suicide in patients attempting to quit smoking with varenicline.

<sup>2</sup> Pasternak et al. had reported high positive predictive value (>90%) for the ICD-10 codes used to identify a schizophrenia-spectrum disorder and a single depressive episode. However, the two conditions are only some of several psychiatric adverse events that the study targeted.



association between varenicline and neuropsychiatric hospitalizations, clinically important psychiatric events that did not include hospitalization (such as a successful suicide without hospitalization) were not captured<sup>2,3,5</sup>. Although the Meyer et al. study<sup>2</sup> also examined a secondary outcome that included outpatient visits with a neuropsychiatric diagnosis, this metric may be simply capturing pre-existing psychiatric comorbidities, rather than treatment emergent psychiatric events. Moreover, a psychiatric episode resulting in discontinuation of smoking cessation drugs without a health care professional encounter would be missed; in light of the stigma that can be attached to psychiatric diagnoses in medical records, particularly in the military, this possibility cannot be ruled out.

Under-ascertainment of outcomes is also a concern with respect to the studies that examined the association between varenicline and suicide/non-fatal self-harm.<sup>1,4</sup> In fact, the Read codes used by GPRD/CPRD have been shown to be unreliable for detecting suicide, and under-report non-fatal self-harm, which undermines the inferential capacity of the Gunnell study because it solely used Read codes to investigate suicide/non-fatal self-harm risk associated with varenicline. We have more confidence in the event count of suicide deaths observed in the Thomas et al. study, because the investigators linked CPRD records to the U.K. mortality data to capture this outcome. The incidence of suicide in the Thomas et al. study's cohort of smokers (27.4 per 100,000 person-years) is about three times the rate obtained from the general CPRD population (9.4 per 100 000 person-years)<sup>10</sup>, which is consistent with findings from prior research that have shown a twofold to threefold higher risk of suicide in smokers versus non-smokers.<sup>11,12</sup> However, Thomas et al. did not compare the rate of suicide deaths among Chantix users to users of another smoking cessation product to obtain a Chantix-associated risk estimate for suicide death. Rather, they compared the rate of suicide death or attempted suicide, a composite outcome, between Chantix users and users of another smoking cessation product. Similar to neuropsychiatric medical encounters, we are concerned about the undercounting of suicide attempts due to the stigma that can be attached to such diagnoses, the difficulty in determining intentionality of injury, and the fact that such attempts are not always brought to medical attention.

Lastly, in the studies that examined the risk of antidepressant initiation,<sup>1,4</sup> prescribing of antidepressants was not a specific measure of incident depression, since antidepressants are also used to treat other disorders, including nonpsychiatric indications.

## 4.2 OTHER DESIGN AND METHODOLOGICAL ISSUES

The study by Pasternak et al. compared risk of neuropsychiatric emergency department visits or hospitalizations between varenicline users and bupropion users; the study found a non-significant 15% lowered risk associated with varenicline use compared with bupropion use (HR: 0.85. 95% CI: 0.55- 1.30; Appendix Table 2, Appendix Figure1). However, given that bupropion also has been associated with psychiatric adverse events and carries a boxed warning alerting about this possibility,<sup>13,14</sup> this finding does not provide reassurance of varenicline's neuropsychiatric safety.

The study by Thomas et al. included data from the timeframe after the publicity of varenicline's neuropsychiatric safety concerns. Adverse publicity may have resulted in patients with a history of neuropsychiatric illness being preferentially prescribed NRT, and healthier patients being preferentially prescribed varenicline (i.e., channeling bias). In fact, varenicline users in the study were indeed less likely to have a history of chronic diseases and psychiatric illness, and had a lower frequency of previous use of hypnotics, antipsychotics, and antidepressants.

After adjusting for baseline characteristics, the all-cause mortality risk at 3 months appeared to be significantly lower among varenicline users than NRT users in two of the three analyses conducted in the Thomas et al. study. The hazard ratio (HR) of 3-month all-cause mortality comparing varenicline to NRT was 0.44 in the Cox regression analysis, and 0.37 in the Propensity score matching analysis (Table 1), which translated to an adjusted risk difference of -1.4 to -2 per 1,000 patients (Table 1 and see the calculation from HRs to risk differences in Appendix I ). Given that three months is too short a timeframe

for realizing the survival benefits of smoking cessation, the reduced risk in all-cause mortality most likely reflects the generally healthier varenicline users than NRT users. Therefore, the risk estimates of the primary outcome (i.e., 3-month suicide and non-fatal self-harm) from those two analyses would likely carry the impact of the residual baseline differences. Their third analysis using an instrumental variable (IV) approach appeared to reduce the impact of residual confounding, because the difference in 3-month mortality risk between varenicline and NRT users became smaller (-0.8 per 1,000 patients, Table 1). IV methods also resulted in a slight increase in 3-month fatal/non-fatal self-harm comparing varenicline users to NRT users (risk difference: 0.4 [95% CI: -0.8-1.5] per 1,000 patients). The change in direction of the risk estimate (from a negative difference to a positive difference) for the primary outcome raise the concern that varenicline use could increase risk of fatal/non-fatal self-harm. Although the observed risk difference is numerically small, it is worth-noting that the possible under-ascertainment of fatal/non-fatal self-harm (as mentioned in section 4.1) would lead to an under-estimate of the risk difference. Nevertheless, given that the risk estimate was not statistically significant, the finding cannot be used to either rule in, or rule out, an association between varenicline use and fatal/non-fatal self-harm.

**Table 1 Findings from the Thomas et al. study**

Analytical approaches	Risk estimate (95% Confidence interval) (Reference: NRT users)	
	3-month suicide and non-fatal self-harm	3-month all-cause mortality
Cox regression analyses	HR: 0.88 (0.52-1.49) Risk difference per 1,000: -0.1 <sup>†</sup>	HR: 0.44* (0.30-0.63) Risk difference per 1,000: -1.4 ~-2 <sup>†</sup>
Propensity score matching analyses	HR: 0.87 (0.51-1.48) Risk difference per 1,000: -0.1 <sup>†</sup>	HR: 0.37* (0.26-0.53) Risk difference per 1,000: ~-2 <sup>†</sup>
Instrumental variable analyses	Risk difference per 1,000: 0.4 (-0.8-1.5)	Risk difference per 1,000: -0.8 (-2.8-1.1)

HR: Hazard ratio

\*p value < 0.05.

<sup>†</sup> see the calculation from HRs to risk differences in Appendix I

## 5 CONCLUSION

Although none of the reviewed observational studies found differences in the risk of serious neuropsychiatric events between varenicline and the reference drug (NRT or bupropion) users, all studies had a number of study design limitations. Most importantly, the outcomes examined in these studies did not cover the full range of the neuropsychiatric adverse events that have been seen in postmarketing spontaneous adverse event reports associated with varenicline. These limitations may underestimate the actual incidence of neuropsychiatric adverse events, and restrict our ability to predict the direction of the relative risk associated with varenicline. Therefore, while these studies appear reassuring, they do not adequately measure the effect of Chantix on the risk of neuropsychiatric adverse events of concern and therefore cannot be interpreted to mean that there is no increased risk of neuropsychiatric events with Chantix.

## 6 RECOMMENDATIONS

The sponsor proposed two main changes to the label: 1) Describing findings of five observational studies in the Warnings and Precautions section to support no evidence of an increased risk of serious neuropsychiatric events with varenicline, compared to NRT or bupropion, 2) Removal of the boxed warning on neuropsychiatric adverse events.

DEPI II does not recommend including the findings of the five observational studies as currently proposed in the label revision, due to the limitations of those studies that were addressed in this review. We also are not inclined to remove the boxed warning at this time because of the concern that such action could be interpreted as confirming “no association” between varenicline use and neuropsychiatric risk, which is not supported by currently available observational data. Given that the sponsor is conducting a

Phase IV trial to examine varenicline's neuropsychiatric safety, it might be more reasonable to discuss the decision on the boxed warning after the completion of the trial (the target completion date is August 2016), when further information regarding varenicline's neuropsychiatric risk is available. Alternatively, DEPI-II can suggest language for including observational studies in the boxed warning which includes the appropriate interpretation of the studies' findings.

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## APPENDICES

Table 1 Design and methods of the observational studies on varenicline use and neuropsychiatric risk

	<b>The VA Study (unpublished)</b>	<b>Meyers et al.</b>	<b>Pasternak et al.</b>	<b>Gunnel et al.</b>	<b>Thomas et al.</b>
Design	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Time frame	May 01 2006 to Sep 30 2007	Aug 01 2006 to Aug 31 2007	Jan 1 2007 to Dec 31 2010	Sep 01 2006 to May 31 2008	Sep 01 2006 to Oct 31 2011
Data sources	VA health care data bases (claims and administrative data)	Military health system data (Claims and administrative data)	Nation-wide linked health care data in Denmark including information on prescription drug use, emergency department visit, hospital admission, neuropsychiatric diagnosis, etc.	UK General Practice Research Database (GPRD), subsequently known as the Clinical Practice Research Datalink (CPRD) (Electronic health care records including demographic, consultation, prescribing, referral and health outcome data from ~500 General Practices)	UK CPRD linked to Office for National Statistics (ONS) mortality data and Health Episode Statistics (HES) data
Exposure	Varenicline or NRT	Varenicline or NRT	Varenicline or bupropion	Varenicline, bupropion, or NRT	Varenicline, bupropion, or NRT
Reference group	NRT	NRT	Bupropion	NRT	NRT
Main Outcomes	30-day Neuropsychiatric hospitalizations <ul style="list-style-type: none"> <li>hospitalization with a primary discharge diagnosis from among the ICD-9 codes of the following conditions: <ul style="list-style-type: none"> <li>Comprehensive mental health disorders</li> <li>Acute composite</li> </ul> </li> </ul>	30-day Neuropsychiatric hospitalizations <ul style="list-style-type: none"> <li>Primary definition: hospitalization with a primary discharge diagnosis from among the ICD-9 codes of the following conditions: <ul style="list-style-type: none"> <li>Drug-induced mental disorders</li> </ul> </li> </ul>	30-day Neuropsychiatric emergency department visits or hospitalizations with a primary diagnosis of the following diagnosis identified using ICD-10 codes <ul style="list-style-type: none"> <li>Mood disorder</li> <li>Psychotic disorder</li> <li>Substance abuse</li> </ul>	90-day Suicide, non-fatal self-harm*, depression, all-cause mortality <ul style="list-style-type: none"> <li>Suicide, non-fatal self-harm and all-cause mortality were identified by relevant diagnoses codes (Read codes) and Oxford Medical</li> </ul>	90-day Suicide, non-fatal self-harm, depression, all-cause mortality <ul style="list-style-type: none"> <li>Suicide was defined as death from suicide in the ONS mortality database, using ICD-10 codes of intentional self-harm and</li> </ul>

	<p>mental health disorders</p> <ul style="list-style-type: none"> <li>• Depression</li> <li>• Schizophrenia</li> <li>• Bipolar disorder</li> <li>• Suicide attempt</li> <li>• Psychosis excluding bipolar, depression and schizophrenia</li> </ul>	<ul style="list-style-type: none"> <li>• Transient mental disorders</li> <li>• Schizophrenia</li> <li>• Episodic and mood disorders</li> <li>• Delusional disorders</li> <li>• Other nonorganic psychoses</li> <li>• Anxiety disorders</li> <li>• Personality disorders</li> <li>• Posttraumatic stress disorder (PTSD)</li> <li>• Depressive disorders</li> <li>• Suicide attempt.</li> <li>• Secondary definition: hospitalization with a neuropsychiatric condition in any discharge diagnoses, or, any neuropsychiatric diagnoses in outpatient records that occurred twice on different days</li> </ul>	<ul style="list-style-type: none"> <li>• Neurotic, stress-related or somatoform disorder</li> <li>• Behavioral syndromes associated with physiological disturbances and physical factors, disorders of adult personality and behavior</li> <li>• unspecified mental disorder, confusion, hallucinations,</li> <li>• symptoms and signs involving emotional state and symptoms and signs involving appearance and behavior</li> </ul>	<p>Information System (OXMIS) medical terms.</p> <ul style="list-style-type: none"> <li>• No death certificates were obtained for any deaths.</li> <li>• Depression was defined as the initiation of antidepressant therapy and excluded patients who had been prescribed antidepressants at any time in the six months before starting smoking cessation therapy</li> </ul>	<p>undetermined deaths</p> <ul style="list-style-type: none"> <li>• Non-fatal self-harm was identified from hospital admission for self-harm from the HES data</li> <li>• Depression was defined as the initiation of antidepressant therapy</li> </ul>
Study population	<p>Primary: New users of varenicline or NRT (no smoking cessation medicine for 12 months) during the study timeframe and matched in a 1:1 ratio by propensity scores</p>	<p>New users (17+ years-old) of varenicline and NRT patch (no smoking cessation medicine for 6 months) during the study time frame and matched 1:1 by propensity scores</p>	<p>New users (18+ years-old) of varenicline and bupropion during the study time frame and matched 1:1 by propensity scores</p>	<p>Users (18+ years-old) of varenicline, bupropion, or NRT during the study timeframe</p>	<p>Primary: New users (18+ years-old) of varenicline, bupropion, and NRT (no smoking cessation medicine for 12 months) during the study timeframe</p>

	Secondary: Prevalent users of NRT who initiated varenicline or continue on NRT during the study timeframe, matched on 1:2 ratio by propensity score				Secondary: First-time users of varenicline, bupropion and NRT during the study timeframe (no prior use of smoking cessation medicines in the database)
Follow-up	Follow-up continued for 30 days after this prescription with censoring for death, end of study periods or event, whichever came first	Follow-up continued for 30 days after this prescription with censoring for deployment, stationing overseas, loss of MHS eligibility, death or event, whichever came first	Follow-up started from the date when the first prescription was filled and censored at the respective date of death, disappearance, immigration, end of study (31 December 2010), switching to the other study drug or psychiatric adverse event, whichever occurred first	Follow-up continued for 90 days after first prescription with censoring for death, starting another smoking cessation drugs, left the practice, primary event (suicide or non-fatal self-harm), whichever came first	Follow-up continued for 90 days after first prescription with censoring for death, left the practice, primary event (suicide or non-fatal self-harm), end of study period, whichever came first
Analyses	Cox proportional-hazards regression	Cox proportional-hazards regression	Cox proportional-hazards regression	Cox proportional-hazards regression	Cox proportional-hazards regression Propensity score matching and Cox proportional-hazards regression Instrumental variable analysis

\*Non-fatal self-harm: suicide attempt that did not result in death

Table 2 Main study findings of the observational studies on varenicline' s neuropsychiatric risk

Study	Outcome	Analyses	Varenicline (N event/total/IR*)	Reference group		Fully-adjusted Hazard Ratio
				NRT (N event/total/IR*)	Bupropion (N event/total/IR*)	
Meyer et al. 2013	NPS hospitalization (primary diagnosis) in 30 days	New users, PS-matched	16/10,814/18	14/10,814/16	-	1.14 (0.56-2.34)
Meyer et al. 2013	NPS hospitalization (any diagnosis) in 30 days	New users, PS-matched	34/10,710/39	43/10710/49	-	0.79 (0.50-1.24)
Meyer et al. 2013	NPS Outpatients visits in 30 days	New users, PS-matched	234/10710/269	327/10710/378	-	0.71 (0.60-0.84)
VA study	NPS hospitalization (primary diagnosis) in 30 days	New users, PS-matched	16/14,131/16	21/14,131/21	-	0.76 (0.40-1.46)
VA study	NPS hospitalization (primary diagnosis) in 30 days	Prevalent users, PS-matched	29/12,258/29	94/24,185/47	-	0.74 (0.49-1.14)
Pasternak et al.	NPS emergency room visit or hospitalization in 30 days	New users, PS-matched	39/17,975/27	-	46/17,935/31	0.85 (0.55-1.30)
Gunnell et al. 2009	Suicide or non-fatal self-harm in 90 days	Prevalent users	18/10,973/5.3*	141/63,265/7.5*	-	1.12† (0.67-1.88)
Gunnell et al. 2009	Suicide thoughts in 90 days	Prevalent users	5/10,973/NA	30/63,265/NA	-	1.43† (0.53-3.85)
Thomas et al. 2013	Suicide or non-fatal self-harm in 90 days	New users	19/30,352/3	69/78,407/4	-	0.88& (0.52-1.49)
Gunnell et al. 2009	Initiation of antidepressants in 90 days‡	Prevalent users	292/9162/NA	1792/49415/NA	-	0.88† (0.77-1.00)
Thomas et al. 2013	Initiation of antidepressants in 90 days*	New users	255/18,386/57	799/42,475/77	-	0.75& (0.65-0.87)

NRT: Nicotine replacement therapy; IR: Incidence Rate=event/1,000 person-year; NPS: neurologic/psychiatric; PS: propensity score

Hazard Ratios calculated using Cox proportional hazards regression model

\*age and sex-standardized

†Adjusted for age; sex; use of hypnotics, antipsychotics, and antidepressants; alcohol misuse; previous suicide related event; previous smoking cessation therapy; psychiatric consultation; date of initial exposure to product, number of general practice visits per year, index of multiple deprivation, UK region.

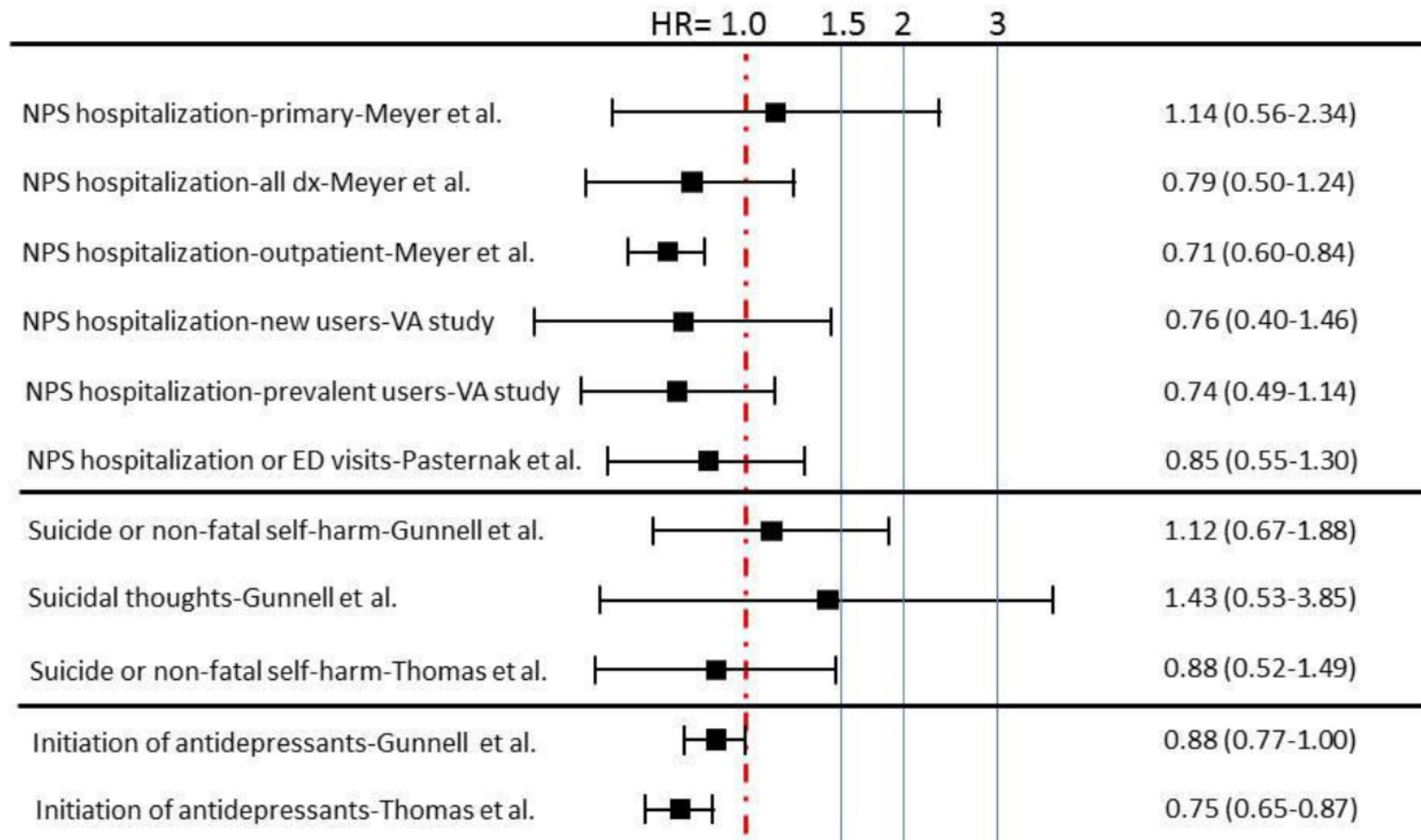
&Adjusted for sex; age; previous psychiatric illness or consultation; previous use of psychotropic drugs such as hypnotics, antipsychotics and antidepressants; previous self-harm; socioeconomic position; major chronic illness; number of general practice consultations in the year before the prescription; exposure to the drug before or after 2008; year of first prescription; and previous use of a smoking cessation product.

‡Restricted to those with no antidepressants in the six months before smoking cessation therapy.

\*Restricted to those with no previous antidepressant use



Figure 1 Forest plot of the main study findings of the observational studies on varenicline' s neuropsychiatric risk



NPS: Neuropsychiatric; ED: Emergency department; HR: Hazard ratio

## Appendix I Calculation of the risk differences of study outcomes based on the hazard ratios of the Cox regression and propensity score matching analyses of the Thomas et al. study

### Fatal and non-fatal self-harm

1. Calculate the crude outcome rates from event counts and follow-up person-time

NRT group	=69/19196*1000	= 3.59 per 1,000 patient-year
Varenicline group	=19/7363*1000	= 2.58 per 1,000 patient-year
  
2. Calculate the adjusted outcome rates from the crude outcome rates and risk ratios of COX regression or PS matching
  - Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression

NRT group	=3.59 * 1	= 3.59
Varenicline group	=3.59 * (0.88)	= 3.16
  
  - Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of COX regression

Varenicline group	=2.58 * 1	= 2.58
NRT group	=2.58 / 0.88	= 2.93
  
  - Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching

NRT group	=3.59 * 1	= 3.59
Varenicline group	=3.59 * (0.87)	= 3.12
  
  - Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching

Varenicline group	=2.58 * 1	= 2.58
NRT group	=2.58 / 0.87	= 2.97
  
3. Calculate the adjusted risk differences between varenicline and NRT reflected by the risk ratio of COX regression or PS matching
  - Adjusted risk differences based on risk ratio of COX regression=

3.16-3.59= -0.43 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months) OR  
2.58-2.93= -0.35 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months)
  - Adjusted risk differences based on risk ratio of COX regression=

3.12-3.59= -0.47 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months) OR  
2.58-2.97= -0.39 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months)

### Mortality

1. Calculate the crude outcome rates from event counts and follow-up person-time

NRT group	=292/19944*1000	= 14.64 per 1,000 patient-year
Varenicline group	=33/7575*1000	= 4.36 per 1,000 patient-year
  
2. Calculate the adjusted outcome rates from the crude outcome rates and risk ratios of COX regression or PS matching
  - Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression

NRT group                     $= 14.64 * 1 = 14.64$   
 Varenicline group         $= 14.64 * (0.44) = 6.44$

**-Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of COX regression**

Varenicline group         $= 4.36 * 1 = 4.36$   
 NRT group                 $= 4.36 / 0.44 = 9.90$

**-Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching**

NRT group                 $= 14.64 * 1 = 14.64$   
 Varenicline group         $= 14.64 * (0.37) = 5.42$

**-Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching**

Varenicline group         $= 4.36 * 1 = 4.36$   
 NRT group                 $= 4.36 / 0.37 = 11.78$

**3. Calculate the adjusted risk differences between varenicline and NRT reflected by the risk ratio of COX regression or PS matching**

**-Adjusted risk differences based on risk ratio of COX regression=**

$6.44 - 14.64 = -8.2$  (per 1,000 patient-year)  $\approx -2.1$  (per 1,000 patients per 3 months) **OR**  
 $4.36 - 9.90 = -5.5$  (per 1,000 patient-year)  $\approx -1.4$  (per 1,000 patients per 3 months)

**-Adjusted risk differences based on risk ratio of PS matching=**

$5.42 - 14.64 = -9.2$  (per 1,000 patient-year)  $\approx -2.3$  (per 1,000 patients per 3 months) **OR**  
 $4.36 - 11.78 = -7.4$  (per 1,000 patient-year)  $\approx -1.9$  (per 1,000 patients per 3 months)

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U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES META-ANALYSIS

**NDA / Serial Number:** 021928 /S-036

**Drug Name:** Chantix (varenicline) tablet; 0.5 mg and 1 mg

**Indication(s):** Aid to smoking cessation

**Applicant:** Pfizer, Inc.

**Date(s):** PDUFA goal date: February 8, 2015

**Review Priority:** Standard

**Biometrics Division:** Division VII

**Statistical Reviewer:** Eugenio Andraca-Carrera, Ph.D.

**Concurring Reviewers:** Mat Soukup, Ph.D., Team Lead, DB VII  
Mark Levenson, Deputy Division Director, DB VII

**Medical Division:** Division of Anesthesia, Analgesia, and Addiction Products

**Clinical Team:** Team Lead: Celia Winchell, M.D.  
Deputy Director of Safety: Judy Racoosin, M.D.

**Project Manager:** Ayanna Augustus

**Keywords:** Smoking cessation, neuropsychiatric safety, meta-analysis

# 1 Executive Summary

Spontaneous reports of adverse events have linked varenicline with a potential increase in neuropsychiatric adverse events. In order to evaluate this risk, the Sponsor conducted a retrospective meta-analysis of randomized clinical trials comparing varenicline relative to placebo. The Sponsor conducted analyses in two sets of trials: a set of 5 clinical trials that captured the risk of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS); and a set of 18 trials that captured neuropsychiatric adverse events through MedDRA codes.

The endpoints in the Sponsor's meta-analysis were:

- Percent of subjects responding “yes” for Suicidal Ideation (any type) and/or Suicidal Behavior (any type) based on the C-SSRS.
- Percent of subjects who experienced an Adverse Event (AE) in the Suicide/Self-injury MedDRA Standardized MedDRA Query (SMQ).
- Percent of subjects who experienced an adverse event in the Hostility/Aggression MedDRA SMQ.
- Percent of subjects who experienced an adverse event in the MedDRA Psychiatric Disorders System Organ Class (SOC).

In addition to these endpoints, the Agency examined the composite endpoint pre-specified in the ongoing trial A3051123 (not included in the meta-analysis), intended to fulfill the PMR requirement issued in 2008. This endpoint includes 241 MedDRA terms for neuropsychiatric events. Analyses of all endpoints were conducted on treatment emergent events, defined as events that occurred while patients were on randomized treatment plus a window of 30 days after treatment discontinuation.

## 1.1 Statistical Issues and Findings

Table 1 shows a summary of the meta-analyses of treatment emergent neuropsychiatric adverse events. These analyses showed no evidence of increased risk associated with varenicline relative to placebo.

The meta-analysis conducted by the Sponsor has the following limitations:

- The suicide/self-injury MedDRA SMQ did not capture some suicide related adverse events when compared to the C-SSRS instrument. It is possible that other MedDRA terms included in the meta-analysis may have also failed to capture neuropsychiatric adverse events of interest.
- 48 out of the 55 events in the analysis of suicidal ideation and behavior based on the C-SSRS instrument were observed in two trials that enrolled patients with a history of schizophrenia or depression. The conclusions of this analysis may or may not be

generalizable to a population without these conditions. Only seven events were observed in the other three trials that collected the C-SSRS.

- MedDRA SMQs and SOC may include adverse events of different severities. It is possible that the SMQs in this meta-analysis may not be adequate to capture and characterize the risk of rare but severe adverse events.

**Table 1. Treatment Emergent Neuropsychiatric Adverse Events**

Endpoint	RR (95% CI)
C-SSRS Suicidal Ideation or Behavior	0.79 (0.46, 1.36)
Suicide / Self-Injury SMQ	0.45 (0.19, 1.07)
Hostility / Aggression SMQ	1.10 (0.60, 2.03)
Psychiatric Disorders SOC	1.03 (0.84, 1.25)
PMR Endpoint	0.85 (0.64, 1.13)

## 2 Introduction

### 2.1 Product Description and Regulatory Background

Chantix (varenicline) was approved by FDA on May 10, 2006 as an aid to smoking cessation. The approved dose regimen is 1-mg twice daily (1 mg BID) for 12 weeks starting with a 1-week titration.

In February of 2009, the label for CHANTIX was modified to add a boxed warning regarding neuropsychiatric events. This change was prompted by spontaneous event reports of adverse events among patients taking CHANTIX. Additional information regarding this risk was also added to section 5.1 WARNINGS and PRECAUTIONS of the label.

On April 8<sup>th</sup>, 2014, Pfizer submitted a meta-analysis for review by the Agency to evaluate the risk of neuropsychiatric adverse events associated with varenicline relative to placebo in two sets of trials:

- A set of 5 Phase III/IV clinical trials that captured the risk of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS). This set of trials is referred to as the “5-Study Cohort”.



- A set of 18 Phase II-IV clinical trials, including the trials in the 5-Study Cohort, which captured psychiatric adverse events through spontaneous adverse events reports coded using the Medical Dictionary for Regulatory Activities (MedDRA).

## 2.2 Trial Database

The trials included in the 5-Study Cohort randomized a total of 1907 patients: 1130 to varenicline and 777 to placebo. These trials had a treatment phase of 12 weeks and off-treatment follow-up ranging from 30 days to 40 weeks. The total duration of these trials varied from 12 weeks + 30 days to 52 weeks. The inclusion criteria and objectives of the trials in the 5-Study cohort were heterogeneous. In particular, trial A3051072 was the only trial in the program that studied patients with a history of schizophrenia and trial A3051122 was the only trial that studied patients with a history of depression.

The 18-Study Cohort includes the 5 trials in the 5-Study Cohort plus 13 additional trials. These trials randomized 5072 patients to varenicline and 3449 patients to placebo. An additional 795 patients in 3 trials were randomized to Zyban. Patients randomized to Zyban were not included in any analyses and will not be discussed further in this review. All trials in the 18-Study Cohort had a treatment phase of 12 weeks, except for the dose ranging trial A3051002, which had a treatment phase of 6 weeks and trial A3051037, which was designed to evaluate long-term safety and had a treatment phase of 52 weeks. A summary of the design characteristics of the 18 trials in the meta-analysis is shown in Table 2.

Table 2. List of Trials Included in the Meta-Analysis

Study	Population / Goal	Duration	Total follow-up <sup>1</sup>	Sample Size		
		On treatment		Varenicline	Placebo	Zyban
5-Study Cohort						
A3051072	Schizophrenia	12 weeks	24 weeks	84	43	-
A3051095	Flexible quit date	12 weeks	24 weeks	486	165	-
A3051115	Assessment of neuropsychiatric symptoms	12 weeks	12 weeks + 30 days	55	55	-
A3051122	Depression	12 weeks	52 weeks	256	269	-
A3051139	Re-treatment	12 weeks	52 weeks	249	245	-
PHASE 2						
A3051002	Dose-ranging	6 weeks	52 weeks	377	123	126
A3051007	Titration	12 weeks	52 weeks	506	121	-
A3051016	Flexible dosing	12 weeks	52 weeks	157	155	-
A3051037	Long-term safety	52 weeks	52 weeks	251	126	-
A3051046_48	Study in Japan	12 weeks	52 weeks	464	154	-
PHASE 3						
A3051028	Zyban comparison	12 weeks	52 weeks	349	344	329
A3051036	Zyban comparison	12 weeks	52 weeks	343	340	340
A3051045	Taiwan and Korea	12 weeks	24 weeks	126	124	-
A3051049	CV disease	12 weeks	52 weeks	353	350	-
A3051054	COPD	12 weeks	52 weeks	248	251	-
A3051055	Multinational Asian sites	12 weeks	24 weeks	165	168	-
PHASE 4						
A3051080	Africa, Mid-East, S. America	12 weeks	24 weeks	390	198	-
A3051104	Smokeless tobacco	12 weeks	26 weeks	213	218	-
<sup>1</sup> Including duration on treatment			TOTAL	5072	3449	795

## 2.3 Data Sources

The Sponsor compiled the data necessary to conduct analyses of neuropsychiatric adverse events into the following datasets:

- Ae5trm.xpt contained information on neuropsychiatric adverse events in the 5-Study Cohort.
- Aetrim.xpt contained information on neuropsychiatric adverse events in the 18-Study Cohort.
- Tteve.xpt contained the data necessary to conduct time to event analyses of neuropsychiatric adverse events.
- Satrim.xpt contained data for all MedDRA-coded adverse events in the 18-Study Cohort.

The Sponsor submitted a meta-analysis report and a Statistical Analysis Plan together with these datasets. These documents were reviewed by the FDA's biostatistics review team. The latest datasets used in this review were submitted by the Sponsor on August 1<sup>st</sup>, 2014.

The following folder available within the CDER Electronic Document Room (EDR) was used to access these datasets:

<\\Cdsub1\\evsprod\\NDA021928>

The format, content and documentation of the data submitted in support of NDA 21928 were adequate to conduct a statistical review of the meta-analysis of neuropsychiatric adverse events conducted by the Sponsor.

All tables and figures in this review were created by the FDA biostatistics review team using the datasets listed above.

## 3 Statistical Evaluation

The meta-analysis of randomized clinical trials discussed in this document was conducted by the Sponsor to assess the risk of neuropsychiatric adverse events associated with varenicline. This meta-analysis was conducted retrospectively to address the potential signal for adverse events reported in spontaneous reports of this product. The meta-analysis Statistical Analysis Plan (SAP) was not submitted for review by the FDA; it was submitted at the same time as the meta-analysis final report.

Note that this submission is intended to support labeling of safety with no information to support efficacy.

## 3.1 Evaluation of Safety

### 3.1.1 Endpoints

The meta-analysis SAP listed several safety endpoints of interest. Below are the sponsor identified safety endpoints of interest according to the database in which they were evaluated.

#### 3.1.1.1 Five Study Cohort Endpoints

- Percent of patients responding “yes” for suicidal ideation (any type) and/or suicidal behavior (any type) based on the C-SSRS.
- Percent of patients responding “yes” to non-suicidal self-injurious behavior based on the C-SSRS.

The C-SSRS is a questionnaire designed to assess suicidality that has been used extensively in research and clinical practice settings. The adverse events related to suicidal ideation and/or behavior using the C-SSRS in the 5-Study Cohort were collected prospectively.

#### 3.1.1.2 Eighteen Study Cohort Endpoints

- Percent of patients who experienced an Adverse Event (AE) in the Suicide/Self-injury MedDRA Standardized MedDRA Query (SMQ).
- Percent of patients who experienced an adverse event in the Hostility/Aggression MedDRA SMQ.
- Percent of patients who experienced an adverse event in the MedDRA Psychiatric disorders system organ class (SOC).

The MedDRA preferred terms that comprise the suicide/self-injury SMQ, the hostility/aggression SMQ and the psychiatric disorders SOC are listed in the Appendix. These composite endpoints include adverse events of all severities, ranging from mild to severe or fatal. These adverse events were not pre-specified endpoints of interest in the 18 trials and were collected through routine reports of adverse events.

#### 3.1.1.3 PMR Endpoint

The FDA review team considered an additional endpoint that was not included in the Sponsor’s submission. This endpoint is based on the primary endpoint pre-specified in trial A3051123 which is an ongoing randomized controlled trial, intended to fulfill the post-marketing requirement (PMR) issued in 2008. This trial is designed to assess the neuropsychiatric safety of varenicline relative to placebo in patients with a history of psychiatric disorders. This trial, still under way, is not included in the meta-analysis discussed in this document.

The primary pre-specified safety endpoint in trial A3051123 is a composite of “*at least one treatment emergent “severe” adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent “moderate” or “severe” adverse event of: agitation, aggression, delusions, hallucinations, homicidal*

*ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide.*” Overall, this endpoint includes 241 MedDRA terms in the 16 components listed in the definition quoted above. These terms were collected as part of routine reports of adverse events in the 18-Study Cohort and were not blindly adjudicated. This endpoint will be referred to as the “Post-marketing requirement (PMR) endpoint”. Note that this endpoint only includes adverse events above a pre-defined threshold of severity for each type of event.

### 3.1.2 Statistical Methodologies

This section describes the methodology used by the Sponsor to conduct their meta-analyses. The FDA review team reproduced the Sponsor’s analyses using the same methodology unless noted otherwise.

Suicidal ideation and behavior captured in the C-SSRS were analyzed through a Poisson regression model with study, treatment group and pre-dose history of suicidal ideation as covariates and the natural logarithm of the time at risk as an offset. The parameter of interest was the risk ratio (RR) of the C-SSRS endpoints comparing patients randomized to varenicline to patients randomized to placebo.

Neuropsychiatric adverse events coded as MedDRA terms were analyzed by the Sponsor through the Mantel-Haenszel risk ratio and its corresponding 95% confidence interval comparing varenicline to placebo. This approach was used to analyze the Suicide/Self Injury SMQ, Hostility/Aggression SMQ and Psychiatric disorders SOC. The implementation of the Mantel-Haenszel risk ratio by the FDA review team was different from the Sponsor’s implementation. We used model weights based on the total number of events and the total number of patient-years of exposure on treatment plus 30 days within each trial, whereas the Sponsor used weights using only the number of events observed in the placebo arm and the patient years of exposure on varenicline divided by the total years of exposure in each trial. Both approaches produced similar estimates of the risk ratio.

The FDA review team analyzed the PMR endpoint through the Mantel-Haenszel risk ratio and its corresponding 95% confidence interval comparing varenicline to placebo based on treatment emergent outcomes and exposure.

The Mantel-Haenszel risk ratio only uses information from trials with at least one reported event. In order to assess the impact of trials with zero events on estimates of risk, we estimated the Mantel-Haenszel risk difference associated with varenicline relative to placebo for each of the endpoints of interest based on treatment emergent outcomes and exposure. The risk difference uses information from all trials, including those with no reported events.

All confidence intervals were calculated at a nominal 95% confidence level. No corrections were made for multiple comparisons.

For each safety endpoint, the primary set of analyses were conducted on treatment emergent events, defined as events that occurred while patients were on randomized treatment plus a window of 30 days after treatment discontinuation (i.e. this is referred to as an on-treatment analysis). Secondary analyses were conducted on events observed during the full follow-up time in each trial (i.e. this is referred to as an on-study analysis).

### 3.1.4 Patient Disposition, Demographics and Baseline Characteristics

#### 3.1.4.1 Demographics and Baseline Characteristics

Table 3 shows pooled baseline demographic characteristics as well as history of smoking, alcohol use and suicidal ideation for subjects randomized to varenicline or placebo in the 18 trials in the meta-analysis. Overall, the majority of subjects were male, had a mean age of approximately 45 years at baseline, and a majority of subjects were categorized as White. All the characteristics summarized in this table appear balanced between the two treatment arms.

**Table 3. Pooled Baseline Characteristics of Patients in the 18 Trials**

	<b>Varenicline</b> (N = 5072 )	<b>Placebo</b> (N = 3449 )
<b>Percent female</b>	35.8%	39.6%
<b>Age ± SD (years)</b>	44.7 ± 12.2	45.5 ± 12.3
≤ 30 years	14.4%	13.0%
31 – 45 years	37.0%	36.7%
46 - 60 years	38.5%	38.6%
> 60 years	10.1%	11.7%
<b>Race</b>		
White	66.8%	69.8%
Black	6.4%	6.6%
Asian	18.8%	16.0%
Other	8.0%	7.6%
<b>History of suicidal ideation</b>	15.3%	15.4%
<b>Mean cigarettes per day in last month ± SD</b>	22.4 ± 9.7	22.3 ± 9.5
<b>Patient drinks alcohol</b>		
Yes	22.0%	20.8%
No	14.6%	13.6%
Missing	63.4%	65.6%
<b>Has tried quitting smoking</b>		
Using counseling	7.6%	7.6%
Using cold turkey	19.7%	19.2%
Using gum	13.5%	12.1%
Using lozenge	1.8%	2.2%

### 3.1.4.2 Follow-Up and Trial Disposition

Table 4 and Table 5 show the mean observed follow-up time on treatment and on study for patients enrolled in the trials included in the meta-analysis. The mean follow-up times were similar for patients randomized to varenicline or placebo.

**Table 4. Mean Follow-up (days) On Treatment + 30 Days**

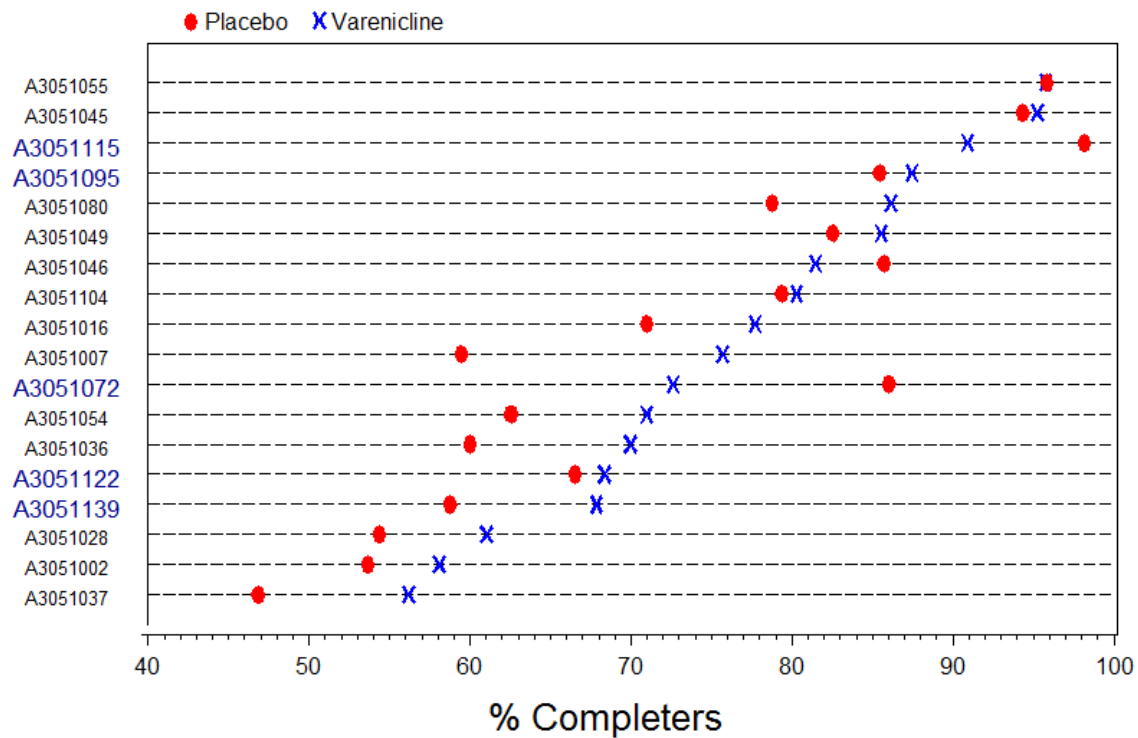
	Varenicline	Placebo
18 -Study Cohort	110	106
5 - Study Cohort	105	102

**Table 5. Mean Follow-up (days) On Study**

	Varenicline	Placebo
18 -Study Cohort	254	240
5 - Study Cohort	224	236

Figure 1 shows that patients randomized to varenicline were on average more likely to complete trial participation than patients randomized to placebo. The two exceptions in which patients on varenicline discontinued study enrollment at a higher rate than patients on placebo were trial 1072 (population with history of schizophrenia) and trial 1115 (assessment of neuropsychiatric symptoms). The pooled study discontinuation rate in the 18 trials was 29% on placebo and 24% on varenicline. A similar pattern was observed regarding treatment discontinuation (not shown in figures): patients randomized to varenicline were on average more likely to remain on randomized treatment than patients randomized to placebo.

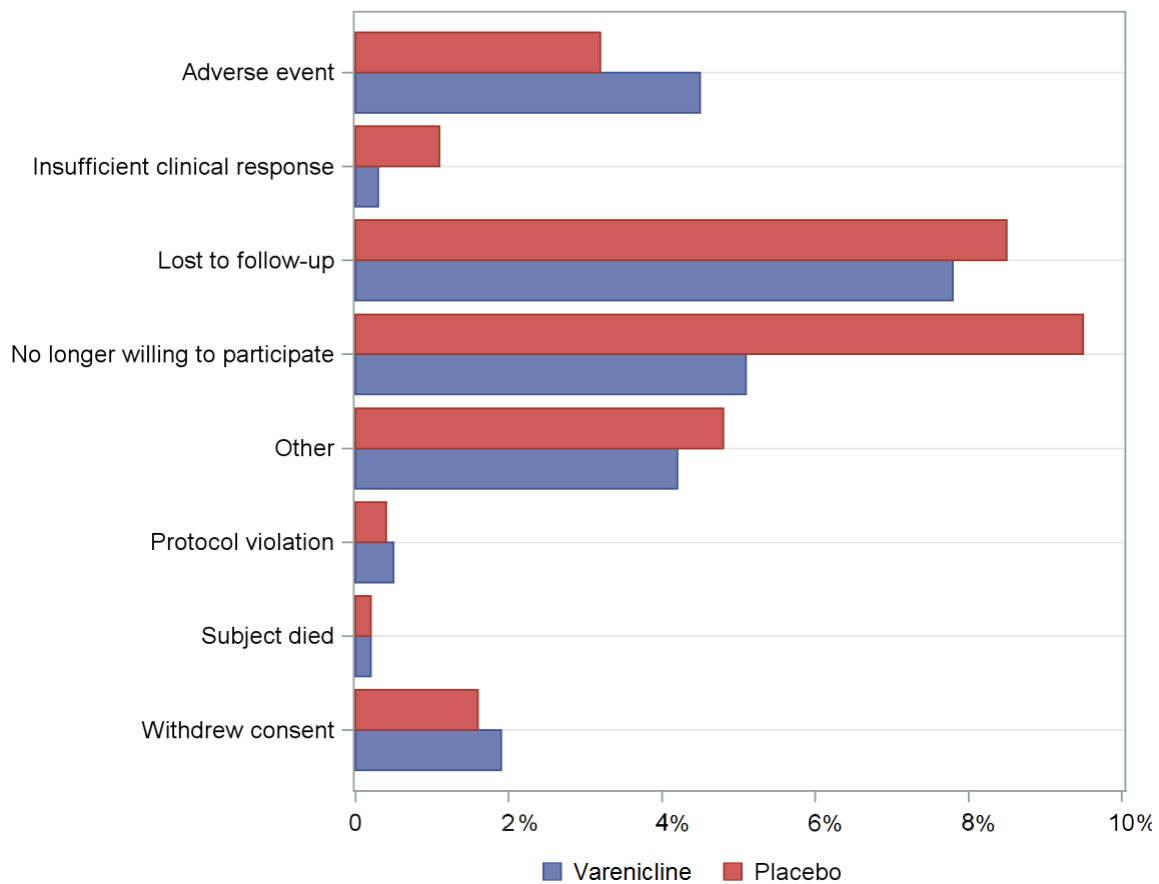
**Figure 1. Study Completers by Study**



A pooled summary of the reasons given for trial discontinuation in the 18 trials in the meta-analysis is shown in Figure 2. Patients randomized to varenicline were more likely to discontinue study participation due to adverse events than patients randomized to placebo. Patients randomized to placebo were more likely to discontinue study participation due to being “no longer willing to participate” or being lost to follow-up. The observed rate of adverse events in the psychiatric disorders SOC events was similar between study completers and non-completers during their recorded follow-up time (not shown in tables).



**Figure 2. Reason for Trial Discontinuation**



### 3.1.3 Analysis Results

This section presents the analyses of the treatment emergent endpoints listed in Section 3.1.1.

#### 3.1.4.1 Suicidal ideation and/or suicidal behavior based on the C-SSRS

Figure 3 shows that 28 out of 1130 (2.5%) patients randomized to varenicline (with 325 patient-years of exposure) and 27 out of 777 (3.5%) patients randomized to placebo (with 217 patient-years of exposure) reported treatment emergent suicidal ideation or behavior based on the C-SSRS instrument in the 5-Study Cohort. The corresponding estimated risk ratio and 95% confidence interval for this endpoint was 0.79 (0.46, 1.36). Table 6 shows that most of these events were recorded as suicidal ideation and only two patients recorded suicidal behavior. One patient randomized to varenicline experienced both suicidal ideation and suicidal behavior.

Forty eight (48) out of the 55 patients with suicidal ideation or behavior were enrolled in two trials: A3051072, which enrolled patients with a history of schizophrenia, and A3051139, which enrolled patients with a history of depression. Only seven events were observed in the other three trials that used the C-SSRS instrument.

Figure 3. Suicidal Ideation or Behavior based on C-SSRS

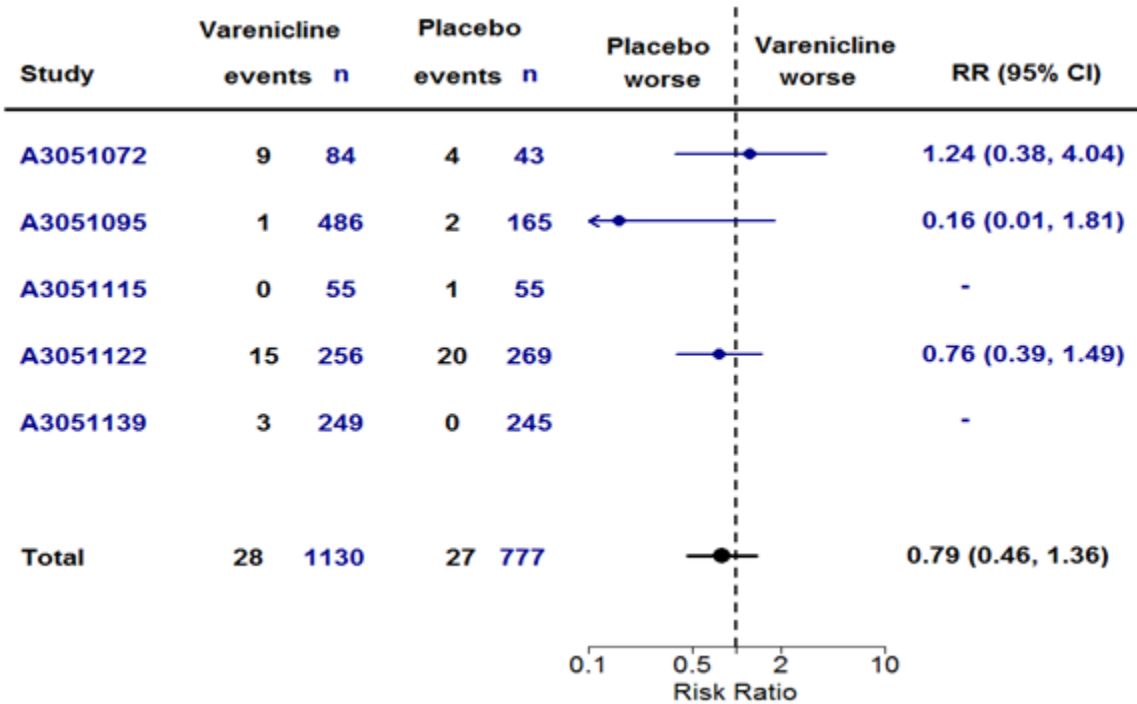


Table 6. Suicidal Ideation and Suicidal Behavior based on C-SSRS

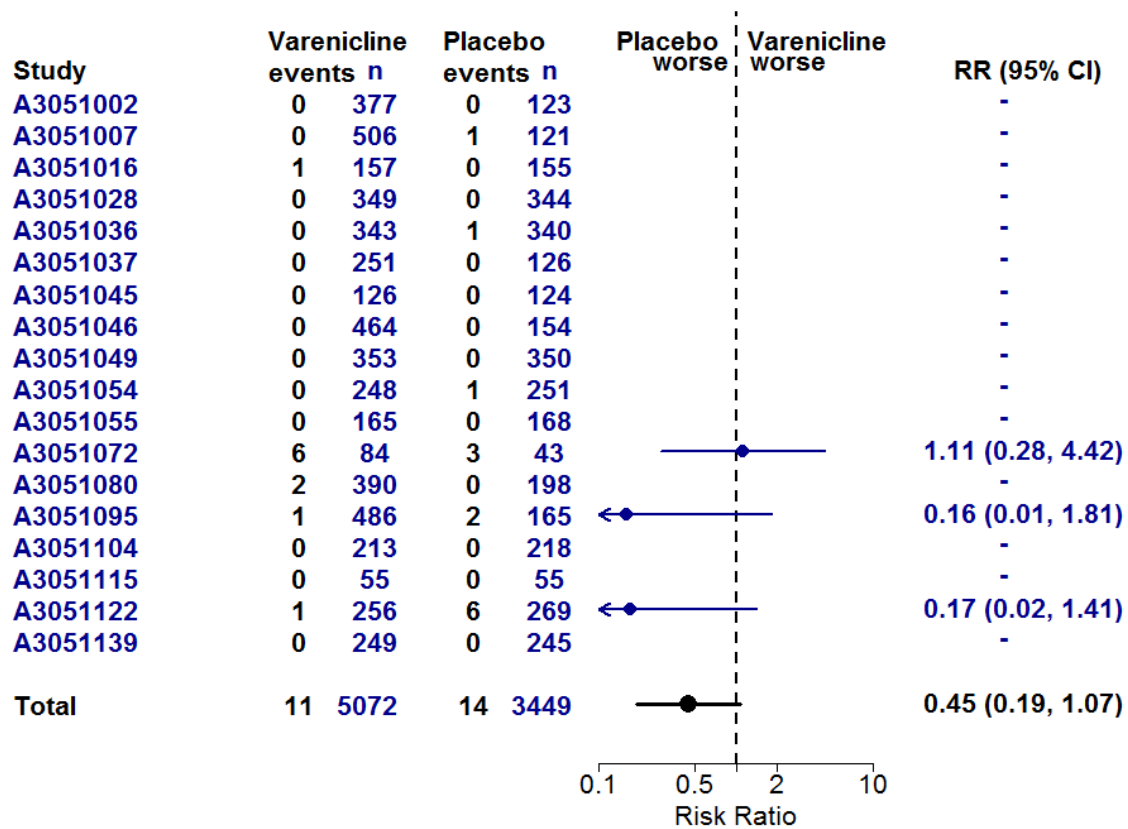
	Varenicline n = 1130	Placebo n = 777	Risk Ratio 95% CI
Suicidal Ideation	28 (2.48%)	26 (3.35%)	0.82 (0.48, 1.42)
Suicidal Behavior	1 (0.09%)	1 (0.13%)	*

\*Not calculated due to the low number of events

### 3.1.4.2 Suicide/Self-Injury SMQ

Of the 8521 randomized patients 35 reported a treatment emergent adverse event in the suicide and self-injury SMQ in the 18-Study Cohort: 11 out of 5072 (0.22%) patients randomized to varenicline and 14 out of 3449 (0.41%) patients randomized to placebo. Figure 4 shows the corresponding estimated risk ratio (RR) and 95% confidence intervals for these data. The estimated meta-analysis RR for this SMQ was 0.45 (0.19, 1.07). Nine of the 25 events were observed in trial A3051072, which studied a population of patients with history of schizophrenia.

Figure 4. Treatment Emergent Events in the Suicide/Self Injury SMQ



In order to evaluate the sensitivity of the suicide and self-injury SMQ, we compared the counts of events of suicidal ideation or behavior captured in the C-SSRS instrument to the adverse events in the suicide and self-injury SMQ in the 5-Study Cohort. These were the only five trials in the meta-analysis that captured suicidal ideation or behavior through both the C-SSRS and MedDRA terms. The results of this comparison are shown in Table 7. There were 37 patients in the 5-Study Cohort with recorded suicidal ideation or behavior in the C-SSRS who did not have an event recorded in the suicide/self-injury SMQ, and one patient with an event in the SMQ who did not have suicidal ideation according to the C-SSRS. Trial A3051122, which enrolled patients with a history of depression, had 28 patients with an event recorded in the C-SSRS but not on the MedDRA suicide and self-injury SMQ.

**Table 7. Comparison of C-SSRS to MedDRA SMQ on Suicidality**

Trial	Suicidality on C-SSRS	Suicidal / Self-Injury SMQ
A3051072	13	9
A3051095	3	3
A3051115	1	0
A3051122	35	7
A3051139	3	0

**Reviewer's Comment:** These inconsistencies may reflect underreporting of adverse events of suicide or self-injury captured through MedDRA coded adverse events that are collected in an unsolicited manner (i.e., patients must voluntarily report them to the study investigator). As such, we recommend that assessment of suicidality by based upon the 5 Study Cohort using the C-SSRS instrument.

### 3.1.4.3 Hostility/Aggression SMQ

A total of 46 patients reported treatment emergent hostility and aggression SMQ events: 28 out of 5072 (0.55%) on varenicline and 18 out of 3449 (0.52%) on placebo. The estimated RR and 95% confidence interval for this SMQ associated with varenicline was 1.10 (0.60, 2.03).

**Figure 5. Treatment Emergent Events in the Hostility/Aggression SMQ**

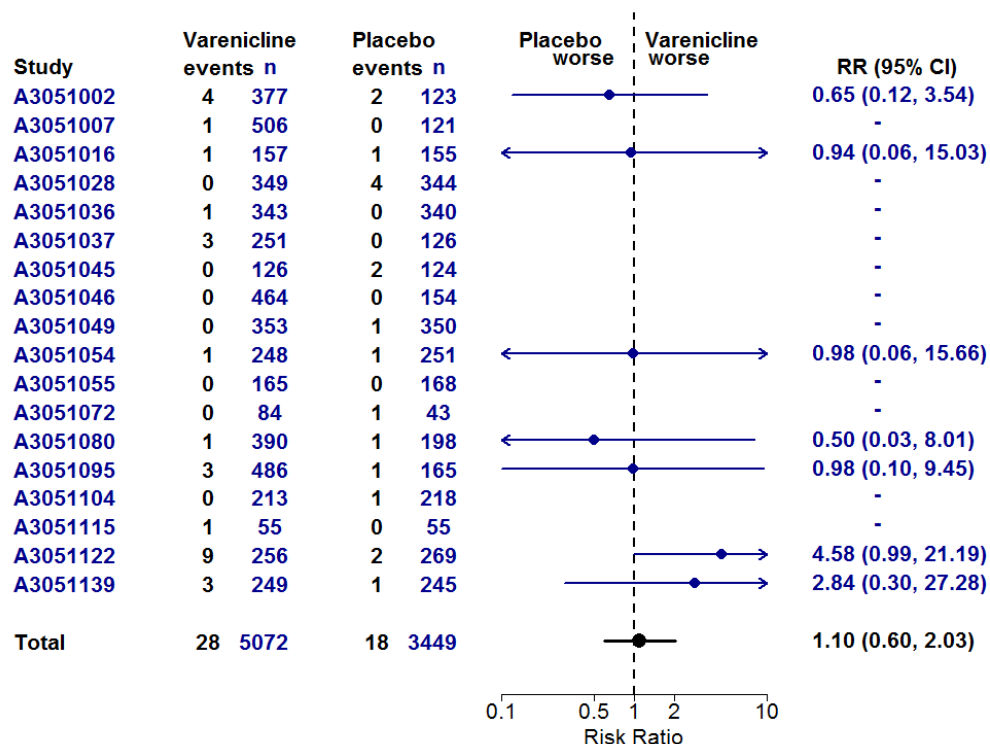


Table 8 shows that all but one of the adverse events in the hostility and aggression SMQ were reported as aggression, anger or hostility. One event was reported as sexual abuse in one patient randomized to varenicline.

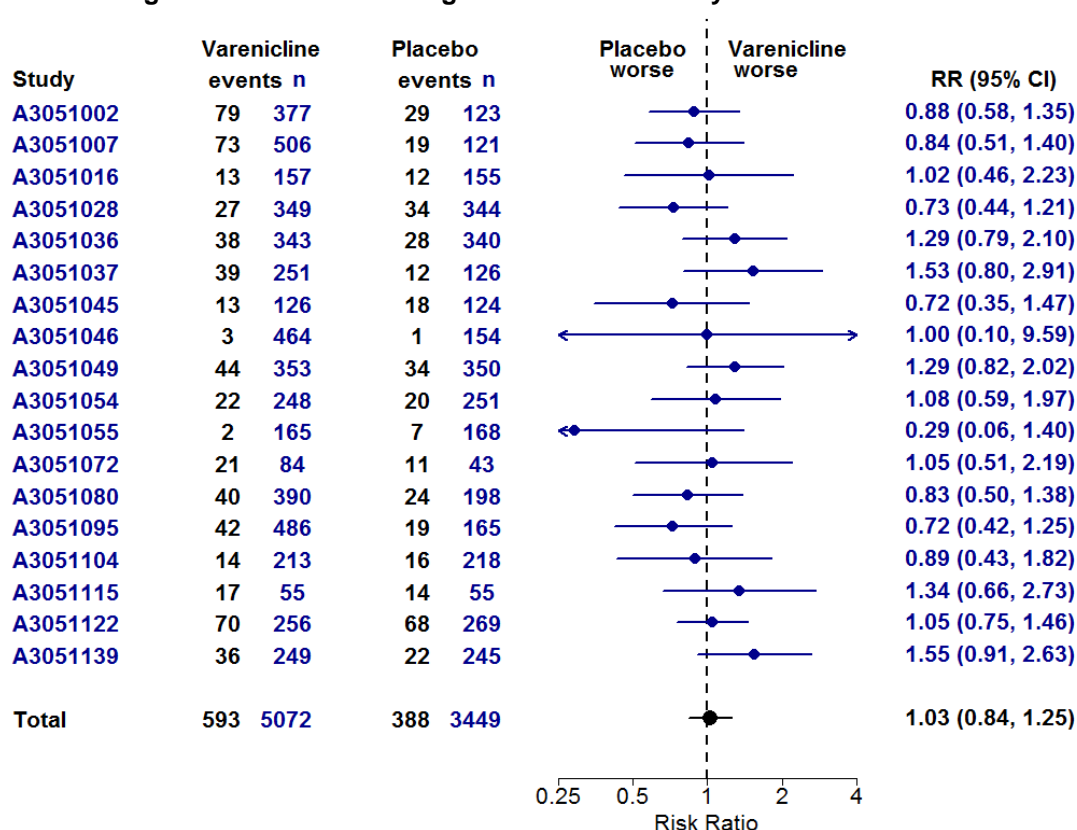
**Table 8. Patients with an Adverse Event in the Hostility/Aggression SMQ**

	<b>Varenicline</b> n = 5072	<b>Placebo</b> n = 3449
<b>Total</b>	<b>28 (0.55%)</b>	<b>18 (0.52%)</b>
Aggression	10 (0.20%)	7 (0.20%)
Anger	12 (0.24%)	12 (0.35%)
Hostility	8 (0.16%)	2 (0.06%)
Sexual Abuse	1 (0.02%)	0

#### **3.1.4.4 Psychiatric Disorders SOC Excluding Sleeping Disorders**

The psychiatric disorders SOC includes events such as anxiety, cognitive disorders, deliria, dementia, depression, mood and personality disorders, sexual dysfunctions, and suicidal behaviors. A total of 981 patients from the 18-Study Cohort had treatment emergent adverse events in this SOC: 593 out of 5072 on varenicline (11.69%) and 388 out of 3449 on placebo (11.25%). The estimated RR and 95% confidence interval for the composite of any event in this SOC, excluding sleeping disorders, associated with varenicline was 1.03 (0.84, 1.25).

Figure 6. Treatment Emergent Events in the Psychiatric Disorders SOC



In Table 9 below, the most common events in the psychiatric disorders SOC were “Anxiety disorders and symptoms” observed in 459 total patients, “Depressed mood disorders and disturbances”, observed in 287 total patients, and “mood disorders and disturbances not elsewhere classified” observed in a total of 169 total patients. The results show a similar incidence of common psychiatric events in patients treated with varenicline compared to patients treated with placebo.

Table 9. Psychiatric Adverse Events Occurring in  $\geq 1\%$  of Patients from Pooled Analysis of 18 Clinical Trials

	Varenicline (N=5072)	Placebo (N=3449)
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)
Depressed mood disorders and disturbances	179 (3.5)	108 (3.1)
Mood disorders and disturbances NEC*	116 (2.3)	53 (1.5)

\* NEC = Not Elsewhere Classified

Counts (percentages) corresponds to the number of patients reporting the event

### 3.1.4.5 PMR Endpoint

The PMR endpoint is a composite that includes 241 MedDRA terms in 16 categories as described in Section 3.1.1. In the 18 trials in the meta-analysis, 146 patients on varenicline (2.9%) and 99 patients in placebo (2.9%) reported at least one treatment emergent event in this composite endpoint. The estimated RR and 95% confidence interval for this endpoint associated with varenicline was 0.85 (0.64, 1.13).

Table 10 shows the categories that comprise the PMR endpoint. The largest number of reported events was reported in the agitation category (132 total events), the mania category (39 events), and the anxiety category (30 events).

**Table 10. Treatment Emergent PMR Endpoint**

	Varenicline n = 5072	Placebo n = 3449
<b>Composite event</b>	<b>146 (2.9%)</b>	<b>99 (2.9%)</b>
<b>Moderate or severe</b>		
Aggression	13 (0.3%)	12 (0.3%)
Agitation	80 (1.6%)	52 (1.5%)
Delusions	0	2 (0.1%)
Hallucination	5 (0.1%)	3 (0.1%)
Mania	28 (0.6%)	11 (0.3%)
Panic	11 (0.2%)	4 (0.1%)
Paranoia	1 (0.0%)	1 (0.0%)
Psychosis	7 (0.1%)	6 (0.2%)
Suicidal ideation / behavior	8 (0.2%)	10 (0.3%)
<b>Severe</b>		
Anxiety	11 (0.2%)	19 (0.6%)
Depression	15 (0.3%)	6 (0.2%)
Feeling abnormal	0	1 (0.0%)

### 3.1.4.6 Sensitivity Analyses Based on Full On-Study Follow-Up Time

The analyses discussed in sections 3.1.4.1 through 3.1.4.5 were conducted on treatment emergent events, defined as events that occurred while patients were on randomized treatment plus a window of 30 days after treatment discontinuation. Table 11 shows the estimated risk ratio for these adverse events based on the full follow-up time from randomization to study completion or discontinuation. These analyses were consistent with the analyses based on treatment emergent adverse events and show no evidence of increased risk of neuropsychiatric adverse events associated with varenicline.

**Table 11. Meta-Analysis Results Based on Full Study Follow-Up Time**

Endpoint	No. Trials	No. of Events (%)		RR (95% CI)
		Varenicline	Placebo	
C-SSRS Suicidal Ideation or Behavior	5	46 (4.07%)	32 (4.12%)	1.11 (0.71, 1.76)
Suicide / Self-Injury SMQ	18	16 (0.32%)	14 (0.41%)	0.67 (0.31, 1.45)
Hostility / Aggression SMQ	18	28 (0.55%)	18 (0.52%)	1.05 (0.57, 1.92)
Psychiatric Disorders SOC	18	618 (12.18%)	400 (11.60%)	0.96 (0.83, 1.11)
PMR endpoint	18	153 (3.02%)	99 (2.87%)	0.90 (0.68, 1.20)

### 3.1.4.7 Sensitivity Analyses – Risk Difference

The Mantel-Haenszel risk ratio estimated in Sections 3.1.4.1 through 3.1.4.6 only uses information from trials with at least one reported event. Trials with no events do not contribute to the estimated risk ratios. In order to assess the impact of trials with zero events on the meta-analysis, we estimated the Mantel-Haenszel risk difference associated with varenicline relative to placebo for each of the endpoints of interest. The risk difference uses information from all trials, including those with no reported events. The results of these analyses are summarized in Table 12. The estimated risk differences show no evidence of increased risk of neuropsychiatric adverse events associated with varenicline relative to placebo.

**Table 12. Risk Difference of Treatment Emergent Neuropsychiatric Adverse Events**

Endpoint	Varenicline N = 5072	Placebo N = 3449	RD per 100 PY (95% CI)
C-SSRS Suicidal Ideation or Behavior	28 (2.5%)	27 (3.5%)	-1.63 (-6.81, 3.55)
Suicide / Self-Injury SMQ	11 (0.22%)	14 (0.41%)	-0.74 (-1.57, 0.09)
Hostility / Aggression SMQ	28 (0.55%)	18 (0.52%)	0.17 (-0.92, 1.27)
Psychiatric Disorders SOC	593 (11.69%)	388 (11.25%)	0.44 (-4.68, 5.57)
PMR endpoint	146 (2.9%)	99 (2.9%)	-1.31 (-3.84, 1.21)



## 4 Summary and Conclusions

### 4.1 Statistical Issues

A potential risk for neuropsychiatric adverse events associated with varenicline has been observed in spontaneous adverse event reports. The Sponsor conducted a meta-analysis of randomized clinical trials to evaluate this risk associated with varenicline relative to placebo. The meta-analysis was conducted in two sets of trials:

- A set of 5 Phase III/IV clinical trials that captured the risk of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS). These five trials randomized 1897 total patients: 1130 to varenicline and 777 to placebo.
- A set of 18 Phase II-IV clinical trials, including the trials in the 5-Study Cohort, which captured psychiatric adverse events through MedDRA codes. These eighteen trials randomized 8521 patients: 5072 to varenicline and 3449 to placebo.

The Sponsor conducted their meta-analysis retrospectively and their Statistical Analysis Plan was not submitted in advance for review by the Agency. The endpoints analyzed by the Sponsor were:

- Percent of subjects responding “yes” for suicidal ideation (any type) and/or suicidal behavior (any type) based on the C-SSRS.
- Percent of subjects who experienced an Adverse Event (AE) in the Suicide/Self-injury MedDRA Standardized MedDRA Query (SMQ).
- Percent of subjects who experienced an adverse event in the Hostility/Aggression MedDRA SMQ.
- Percent of subjects who experienced an adverse event in the MedDRA Psychiatric disorders system organ class (SOC).

The collection of the C-SSRS endpoints in the 5-Study cohort was actively captured using the C-SSRS instrument. The endpoints based on MedDRA terms were collected as part of standard adverse event reports in the eighteen clinical trials in the meta-analysis. In addition to these endpoints, the Agency examined the composite endpoint pre-specified in the ongoing trial A3051123, intended to fulfill the PMR requirement issued in 2008.

The analysis population of interest for all endpoints consisted of the time during which patients were on randomized treatment plus a window of 30 days after treatment discontinuation.

## 4.2 Collective Evidence

Table 13 shows a summary of the estimated risk ratios and corresponding 95% confidence intervals for treatment emergent neuropsychiatric adverse events associated with varenicline. These analyses showed no evidence of increased risk of neuropsychiatric adverse events associated with varenicline relative to placebo.

**Table 13. Summary of Meta-Analysis of Treatment Emergent Adverse Events**

Endpoint	No. Trials	Total events	RR (95% CI)
C-SSRS Suicidal Ideation or Behavior	5	55	0.79 (0.46, 1.36)
Suicide / Self-Injury SMQ	18	25	0.45 (0.19, 1.07)
Hostility / Aggression SMQ	18	46	1.10 (0.60, 2.03)
Psychiatric Disorders SOC	18	981	1.03 (0.84, 1.25)
PMR Endpoint	18	245	0.85 (0.64, 1.13)

The following limitations of the meta-analysis have been discussed in this review:

- All analyses in the 18-Study Cohort were conducted retrospectively. Adverse events of interest were not collected prospectively and therefore it is possible that some adverse events may have been underreported in these trials. Specifically, as shown in Section 3.1.4.2, the suicide/self-injury SMQ did not capture some suicide related adverse events when compared to the C-SSRS instrument. It is possible that other MedDRA terms included in the meta-analysis may have also failed to capture psychiatric adverse events of interest.
- 48 out of the 55 events in the analysis of suicidal ideation and behavior based on the C-SSRS instrument were observed in two trials that enrolled patients with a history of schizophrenia or depression. The conclusions of this analysis may or may not be generalizable to a population without these conditions. Only seven events were observed in the other three trials that collected the C-SSRS.
- MedDRA SMQs and SOCs may include adverse events of different severities. It is possible that the SMQs in this meta-analysis may not be adequate to capture and characterize the risk of rare but severe adverse events.

## Appendix 1. MedDRA SMQs and Psychiatric Disorders SOC

The **Suicide/Self-injury SMQ** includes the following MedDRA Preferred Terms:

- Completed suicide
- Depression suicidal
- Intentional overdose
- Intentional self-injury
- Poisoning deliberate
- Self-injurious behavior
- Self-injurious ideation
- Suicidal behavior
- Suicidal ideation
- Suicide attempt

The **Hostility/Aggression SMQ** includes the following PTs:

- Aggression
- Amygdalotomy
- Anger
- Antisocial behavior
- Antisocial personality disorder
- Belligerence
- Borderline personality disorder
- Child abuse
- Conduct disorder
- Homicidal ideation
- Homicide
- Hostility
- Incest
- Intermittent explosive disorder
- Physical abuse
- Physical assault
- Psychopathic personality
- Sexual abuse
- Violence-related symptoms

The **Psychiatric Disorders System Organ Class**, excluding sleeping disorders, includes the following High Level Group Terms (HLGTs):

- Adjustment disorders (including subtypes)
- Anxiety disorders and symptoms
- Changes in physical activity
- Cognitive and attention disorders and disturbances
- Communication disorders and disturbances
- Deliria (including confusion)
- Dementia and amnestic conditions
- Depressed mood disorders and disturbances
- Developmental disorders NEC

- Dissociative disorders
- Disturbances in thinking and perception
- Eating disorders and disturbances
- Impulse control disorders NEC
- Manic and bipolar mood disorders and disturbances
- Mood disorders and disturbances NEC
- Personality disorders and disturbances in behaviour
- Psychiatric and behavioural symptoms NEC
- Psychiatric disorders NEC
- Schizophrenia and other psychotic disorders
- Sexual dysfunctions, disturbances and gender identity disorders
- Somatoform and factitious disorders
- Suicidal and self-injurious behaviours NEC

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EUGENIO ANDRACA-CARRERA  
09/18/2014

MATTHEW J SOUKUP  
09/18/2014  
Concur

MARK S LEVENSON  
09/18/2014

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CHANTIX safely and effectively. See full prescribing information for CHANTIX.

CHANTIX® (varenicline) Tablets

Initial U.S. Approval: 2006

### **WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS**

*See full prescribing information for complete boxed warning.*

- ~~Serious neuropsychiatric events have been reported in patients taking CHANTIX. (5.1 and 6.2)~~
- ~~Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior while taking CHANTIX or shortly after discontinuing CHANTIX. (5.1 and 6.2)~~
- ~~Weigh the risks of CHANTIX against benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (5.1 and 6.2)~~

## RECENT MAJOR CHANGES

### Highlights of Prescribing Information

Warnings and Precautions, Serious Neuropsychiatric Events 04/2014

### Full Prescribing Information

Warning, Serious Neuropsychiatric Events 04/2014

Warnings and Precautions, Neuropsychiatric Symptoms  
and Suicidality (5.1) 04/2014

02/2013  
Cardiovascular Events (5.4) 12/2012

## INDICATIONS AND USAGE

CHANTIX is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment. (1 and 2.1)

## DOSAGE AND ADMINISTRATION

- Begin CHANTIX dosing one week before the date set by the patient to stop smoking. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment. (2.1)
- Starting week: 0.5 mg once daily on days 1-3 and 0.5 mg twice daily on days 4-7. (2.1)
- Continuing weeks: 1 mg twice daily for a total of 12 weeks. (2.1)
- An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence. (2.1)
- Renal impairment: Reduce the dose in patients with severe renal impairment (estimated creatinine clearance <30 mL/min). (2.2)
- Consider dose reduction for patients who cannot tolerate adverse effects. (2.1)
- Another attempt at treatment is recommended for those who fail to stop smoking or relapse when factors contributing to the failed attempt have been addressed. (2.1)
- Provide patients with appropriate educational materials and counseling to support the quit attempt. (2.1)

## DOSAGE FORMS AND STRENGTHS

Tablets: 0.5 mg and 1 mg (3)

## CONTRAINDICATIONS

History of serious hypersensitivity or skin reactions to CHANTIX (4)

## WARNINGS AND PRECAUTIONS

- **Serious Neuropsychiatric Events:** Serious neuropsychiatric events have been reported in patients taking CHANTIX.
- **Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior while taking CHANTIX or shortly after discontinuing CHANTIX.**
- **Weigh the risks of CHANTIX against benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (See Full Prescribing Information for complete warning, 5.1 and 6.2).**
- **Angioedema and hypersensitivity reactions:** Such reactions, including angioedema, infrequently life threatening, have been reported. Instruct patients to discontinue CHANTIX and immediately seek medical care if symptoms occur. (5.2 and 6.2)
- **Serious skin reactions:** Rare, potentially life-threatening skin reactions have been reported. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions. (5.3 and 6.2)
- **Cardiovascular events:** A meta-analysis of 15 clinical trials, including a trial in patients with stable cardiovascular disease, demonstrated that while cardiovascular events were infrequent overall, some were reported more frequently in patients treated with CHANTIX. These events occurred primarily in patients with known cardiovascular disease. In both the clinical trial and meta-analysis, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX. Instruct patients to notify their health-care providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke. (5.4 and 6.1)
- **Accidental injury:** Accidental injuries (e.g., traffic accidents) have been reported. Instruct patients to use caution driving or operating machinery until they know how CHANTIX may affect them. (5.5)
- **Nausea:** Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (5.6)

## ADVERSE REACTIONS

Most common adverse reactions (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

## DRUG INTERACTIONS

- Other smoking cessation therapies: Safety and efficacy in combination with other smoking cessation therapies has not been established. Coadministration of varenicline and transdermal nicotine resulted in a high rate of discontinuation due to adverse events. (7.1)
- Effect of smoking cessation: Pharmacokinetics or pharmacodynamics of certain drugs may be altered due to smoking cessation with CHANTIX, necessitating dose adjustment. (7.2)

## USE IN SPECIFIC POPULATIONS

- **Pregnancy:** CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- **Nursing Mothers:** Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
- **Pediatric Use:** Safety and effectiveness not established (8.4)
- **Renal Impairment:** Dosage adjustment is required for severe renal impairment. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 04/201402/2013

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*\*Sections or subsections omitted from the full prescribing information are not listed.*

## FULL PRESCRIBING INFORMATION

### WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

Serious neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking CHANTIX in the postmarketing experience. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

Data from clinical trials and observational studies have not demonstrated an association between treatment with CHANTIX and serious neuropsychiatric events. A meta-analysis of 5 clinical trials, which used a suicide severity rating scale and included 1907 patients, showed no increase in the incidence of suicidal ideation and/or behavior in patients treated with CHANTIX compared to patients treated with placebo. A meta-analysis of 18 clinical trials, including 8521 patients, showed a similar incidence of overall neuropsychiatric adverse events, other than sleep disorders, in patients treated with CHANTIX compared to patients treated with placebo. Five observational studies showed no evidence of an increased risk of serious neuropsychiatric events in patients treated with CHANTIX compared to patients treated with nicotine replacement therapy or bupropion [see Warnings and Precautions (5.1)].

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients have not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. [see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]

### 1 INDICATIONS AND USAGE

CHANTIX is indicated for use as an aid to smoking cessation treatment.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Usual Dosage for Adults

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Provide patients with appropriate educational materials and counseling to support the quit attempt.

The patient should set a date to stop smoking. Begin CHANTIX dosing one week before this date. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment.

CHANTIX should be taken after eating and with a full glass of water.

The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – end of treatment:	1 mg twice daily

Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks' treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence.

Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

Consider a temporary or permanent dose reduction in patients who cannot tolerate the adverse effects of CHANTIX.

#### 2.2 Dosage in Special Populations

Patients with Impaired Renal Function No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance <30 mL/min), the recommended starting dose of CHANTIX is 0.5 mg once daily. The dose may then be titrated as needed to a maximum dose of 0.5 mg twice a day. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

Elderly and Patients with Impaired Hepatic Function No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken

in dose selection, and it may be useful to monitor renal function [see Use in Specific Populations (8.5)].

### 3 DOSAGE FORMS AND STRENGTHS

Capsular, biconvex tablets: 0.5 mg (white to off-white, debossed with "Pfizer" on one side and "CHX 0.5" on the other side) and 1 mg (light blue, debossed with "Pfizer" on one side and "CHX 1.0" on the other side)

### 4 CONTRAINDICATIONS

CHANTIX is contraindicated in patients with a known history of serious hypersensitivity reactions or skin reactions to CHANTIX

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Neuropsychiatric Symptoms and Suicidality

##### Meta-analyses of clinical trials

Data from clinical trials have not demonstrated an association between treatment with CHANTIX and serious neuropsychiatric events.

A meta-analysis of 5 randomized, double blind, placebo controlled trials, including 1907 patients (1130 CHANTIX, 777 placebo), some of which had psychiatric conditions, was conducted to assess suicidal ideation and behavior as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). The results showed no increase in the incidence of suicidal ideation and/or behavior in patients treated with CHANTIX compared to patients treated with placebo, with a Risk Ratio (RR) of 0.79 (95% Confidence Interval [CI]: 0.46, 1.36), as shown in Table 1.

**Table 1. Number of patients and Risk Ratio for Suicidal Ideation and/or Behavior Reported on C-SSRS from a Meta-Analysis of 5 Clinical Trials Comparing CHANTIX to Placebo**

	CHANTIX (N=1130)	Placebo (N=777)
Patients with Suicidal ideation and/or behavior* [n (%)]**	28 (2.5)	27 (3.5)
Patient-years of exposure	325	217
Risk Ratio <sup>#</sup> (RR; 95% CI)	0.79 (0.46, 1.36)	

\* Includes one patient with suicidal behaviour in each treatment arm

\*\* Patients with events up to 30 days after treatment; % are not weighted by study

<sup>#</sup> RR of incidence rates per 100 patient years

A meta-analysis of 18 double-blind, randomized, placebo-controlled clinical trials, including 8521 patients (5072 CHANTIX, 3449 placebo), some of which had psychiatric conditions, was conducted to assess the neuropsychiatric safety of CHANTIX. The results showed a similar incidence of overall neuropsychiatric adverse events, other than sleep disorders, in patients treated with CHANTIX compared to patients treated with placebo, with a risk ratio (RR) of 1.01 (95% CI: 0.88, 1.15), as shown in Table 2.

**Table 2. Number of Patients and Risk Ratio for Neuropsychiatric Adverse Events other than Sleep Disorders from a Meta-Analysis of 18 Clinical Trials Comparing CHANTIX to Placebo**

	CHANTIX (N=5072)	Placebo (N=3449)
Patients with neuropsychiatric adverse events other than sleep disorders [n (%)]*	593 (11.7)	388 (11.2)
Patient-years of exposure	1558	1023
Relative Risk <sup>#</sup> (RR; 95% CI)	1.01 (0.88, 1.15)	

\* Patients with events up to 30 days after treatment; % are not weighted by study

<sup>#</sup> RR of incidence rates per 100 patient years

##### Observational studies

Five observational studies, which included from 10,000 to nearly 60,000 users of CHANTIX, showed no evidence of an increased risk of serious neuropsychiatric events with CHANTIX compared to nicotine replacement therapy (NRT) or bupropion. Two of these studies were retrospective cohort studies and found no evidence of an increased risk of neuropsychiatric hospitalizations in users of CHANTIX compared to users of NRT patch (Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI]: 0.56–2.34 in the first study and 0.76; 95% CI: 0.40–1.46 in the second study). A third cohort study showed no evidence of an increased risk of fatal or nonfatal self harm (HR of 1.12; 95% CI: 0.67–1.88) or treated depression (HR of 0.88; 95% CI: 0.77–1.00) in CHANTIX users compared to NRT users. A fourth study, a prospective cohort study using the same database as the third study but including nearly 50% more patients, showed no evidence of a higher risk of fatal and non-fatal self harm (HR of 0.88; 95% CI: 0.52–1.49), or treated depression (HR of 0.75; 95% CI: 0.65–0.87) in users of CHANTIX compared to users of NRT. A fifth cohort

study using a national register system, found that CHANTIX was not associated with an increased risk of psychiatric adverse events diagnosed during an emergency department visit or in-patient admission compared to users of bupropion (HR 0.85; 95% CI: 0.55–1.30). All five studies included patients with and without a psychiatric history.

#### Postmarketing Experience

Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX [see ~~Boxed~~ Warning and Adverse Reactions (6.2)]. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients has not been established. Limited data are available from a single smoking cessation study in patients with stable schizophrenia or schizoaffective disorder [see Adverse Reactions (6.1)].

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, depressed mood, changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. ~~In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.~~

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

#### 5.2 Angioedema and Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions including angioedema in patients treated with CHANTIX [see Adverse Reactions (6.2), and Patient Counseling Information (17.10)]. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). There were infrequent reports of life-threatening angioedema requiring emergent medical attention due to respiratory compromise. Instruct patients to discontinue CHANTIX and immediately seek medical care if they experience these symptoms.

#### 5.3 Serious Skin Reactions

There have been postmarketing reports of rare but serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients using CHANTIX [see Adverse Reactions (6.2)]. As these skin reactions can be life-threatening, instruct patients to stop taking CHANTIX and contact a healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.

#### 5.4 Cardiovascular Events

In a placebo-controlled clinical trial of CHANTIX administered to patients with stable cardiovascular disease, with approximately 350 patients per treatment arm, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX, but certain nonfatal cardiovascular events occurred more frequently in patients treated with CHANTIX than in patients treated with placebo [see Clinical Trials Experience (6.1)]. Table 34 below shows the incidence of deaths and of selected nonfatal serious cardiovascular events occurring more frequently in the CHANTIX arm compared to the placebo arm. These events were adjudicated by an independent blinded committee. Nonfatal serious cardiovascular events not listed occurred at the same incidence or more commonly in the placebo arm. Patients with more than one cardiovascular event of the same type are counted only once per row. Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina.



**Table 31. Mortality and Adjudicated Nonfatal Serious Cardiovascular Events in the Placebo-Controlled CHANTIX Trial in Patients with Stable Cardiovascular Disease**

Mortality and Cardiovascular Events	CHANTIX (N=353) n (%)	Placebo (N=350) n (%)
<b>Mortality (Cardiovascular &amp; All-cause up to 52 wks)</b>		
Cardiovascular death	1 (0.3)	2 (0.6)
All-cause mortality	2 (0.6)	5 (1.4)
<b>Nonfatal Cardiovascular Events (rate on CHANTIX &gt; Placebo)</b>		
<i>Up to 30 days after treatment</i>		
Nonfatal myocardial infarction	4 (1.1)	1 (0.3)
Nonfatal Stroke	2 (0.6)	0 (0)
<i>Beyond 30 days after treatment &amp; up to 52 weeks</i>		
Nonfatal myocardial infarction	3 (0.8)	2 (0.6)
Need for coronary revascularization	7 (2.0)	2 (0.6)
Hospitalization for angina pectoris	6 (1.7)	4 (1.1)
Transient ischemia attack	1 (0.3)	0 (0)
New diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure	5 (1.4)	2 (0.6)

A meta-analysis of 15 clinical trials of  $\geq 12$  weeks treatment duration, including 7002 patients (4190 CHANTIX, 2812 placebo), was conducted to systematically assess the cardiovascular safety of CHANTIX. The study in patients with stable cardiovascular disease described above was included in the meta-analysis. There were lower rates of all-cause mortality (CHANTIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHANTIX 2 [0.05%]; placebo 2 [0.07%]) in the CHANTIX arms compared with the placebo arms in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred in the trials included in the meta-analysis, as described in Table 42. These events occurred primarily in patients with known cardiovascular disease.

**Table 42. Number of MACE cases, Hazard Ratio and Rate Difference in a Meta-Analysis of 15 Clinical Trials Comparing CHANTIX to Placebo\***

	CHANTIX N=4190	Placebo N=2812
<b>MACE cases, n (%)</b>	13 (0.31%)	6 (0.21%)
Patient-years of exposure	1316	839
<b>Hazard Ratio (95% CI)</b>	1.95 (0.79, 4.82)	
<b>Rate Difference per 1,000 patient-years (95% CI)</b>	6.30 (-2.40, 15.10)	

\*Includes MACE occurring up to 30 days post treatment.

The meta-analysis showed that exposure to CHANTIX resulted in a hazard ratio for MACE of 1.95 (95% confidence interval from 0.79 to 4.82) for patients up to 30 days after treatment; this is equivalent to an estimated increase of 6.3 MACE events per 1,000 patient-years of exposure. The meta-analysis showed higher rates of CV endpoints in patients on CHANTIX relative to placebo across different time frames and pre-specified sensitivity analyses, including various study groupings and CV outcomes. Although these findings were not statistically significant they were consistent. Because the number of events was small overall, the power for finding a statistically significant difference in a signal of this magnitude is low.

CHANTIX was not studied in patients with unstable cardiovascular disease or cardiovascular events occurring within two months before screening. Patients should be advised to notify a health-care provider of new or worsening symptoms of cardiovascular disease. The risks of CHANTIX should be weighed against the benefits of its use in smokers with cardiovascular disease. Smoking is an independent and major risk factor for cardiovascular disease. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo.

## 5.5 Accidental Injury

There have been postmarketing reports of traffic accidents, near-miss incidents in traffic, or other accidental injuries in patients taking CHANTIX. In some cases, the patients reported somnolence, dizziness, loss of consciousness or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. Advise patients to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

## 5.6 Nausea

Nausea was the most common adverse reaction reported with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some patients, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. For patients treated to the maximum recommended dose of 1 mg twice daily following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking CHANTIX 0.5 mg twice daily following initial titration, the incidence was 16% compared with 11% for placebo. Approximately 3% of patients treated with CHANTIX 1 mg twice daily in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, a dose reduction should be considered.

## 6 ADVERSE REACTIONS

The following serious adverse reactions were reported in postmarketing experience and are discussed in greater detail in other sections of the labeling:

- Neuropsychiatric symptoms and suicidality [see **Boxed Warning and Warnings and Precautions** (5.1)]
- Angioedema and hypersensitivity reactions [see **Warnings and Precautions** (5.2)]
- Serious skin reactions [see **Warnings and Precautions** (5.3)]
- Accidental injury [see **Warnings and Precautions** (5.5)]

In the placebo-controlled studies, the most common adverse events associated with CHANTIX (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.

The treatment discontinuation rate due to adverse events in patients dosed with 1 mg twice daily was 12% for CHANTIX, compared to 10% for placebo in studies of three months' treatment. In this group, the discontinuation rates that are higher than placebo for the most common adverse events in CHANTIX-treated patients were as follows: nausea (3% vs. 0.5% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo).

Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness.

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During the premarketing development of CHANTIX, over 4500 subjects were exposed to CHANTIX, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less.

The most common adverse event associated with CHANTIX treatment is nausea, occurring in 30% of patients treated at the recommended dose, compared with 10% in patients taking a comparable placebo regimen [see **Warnings and Precautions** (5.6)].

Table 53 shows the adverse events for CHANTIX and placebo in the 12-week fixed dose studies with titration in the first week [Studies 2 (titrated arm only), 4, and 5]. Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

MedDRA High Level Group Terms (HLGT) reported in  $\geq 5\%$  of patients in the CHANTIX 1 mg twice daily dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in  $\geq 1\%$  of CHANTIX patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as 'Insomnia', 'Initial insomnia', 'Middle insomnia', 'Early morning awakening' were grouped, but individual patients reporting two or more grouped events are only counted once.

**Table 53: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (HLGTs  $\geq 5\%$  of patients in the 1 mg BID CHANTIX Group and more commonly than placebo and PT  $\geq 1\%$  in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more**

than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	CHANTIX 0.5 mg BID N=129	CHANTIX 1 mg BID N=821	Placebo N=805
<b>GASTROINTESTINAL (GI)</b>			
GI Signs and Symptoms			
Nausea	16	30	10
Abdominal Pain *	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4
<b>PSYCHIATRIC DISORDERS</b>			
Sleep Disorder/Disturbances			
Insomnia **	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
<b>NERVOUS SYSTEM</b>			
Headaches			
Headache	19	15	13
Neurological Disorders			
NEC			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
<b>GENERAL DISORDERS</b>			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
<b>RESPIR/THORACIC/MEDI AST</b>			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0
Dyspnea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
<b>SKIN/SUBCUTANEOUS TISSUE</b>			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritis	0	1	1
<b>METABOLISM &amp; NUTRITION</b>			
Appetite/General Nutrit. Disorders			
Increased appetite	4	3	2
Decreased appetite/ Anorexia	1	2	1

\* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort

\*\* Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern and frequency of adverse events during the longer-term trials was similar to those described in Table 33, though several of the most common events were reported by a greater proportion of patients with long-term use (e.g., nausea was reported in 40% of patients treated with CHANTIX 1 mg twice daily in a one-year study, compared to 8% of placebo-treated patients).

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which

were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

**Blood and Lymphatic System Disorders.** *Infrequent* anemia, lymphadenopathy. *Rare* leukocytosis, splenomegaly, thrombocytopenia.

**Cardiac Disorders.** *Infrequent* angina pectoris, arrhythmia, bradycardia, myocardial infarction, palpitations, tachycardia, ventricular extrasystoles. *Rare* acute coronary syndrome, atrial fibrillation, cardiac flutter, cor pulmonale, coronary artery disease.

**Ear and Labyrinth Disorders.** *Infrequent* tinnitus, vertigo. *Rare* deafness, Meniere's disease.

**Endocrine Disorders.** *Infrequent* thyroid gland disorders.

**Eye Disorders.** *Infrequent* conjunctivitis, dry eye, eye irritation, eye pain, vision blurred, visual disturbance. *Rare* acquired night blindness, blindness transient, cataract subcapsular, ocular vascular disorder, photophobia, vitreous floaters.

**Gastrointestinal Disorders.** *Frequent* diarrhea. *Infrequent* dysphagia, enterocolitis, eructation, esophagitis, gastritis, gastrointestinal hemorrhage, mouth ulceration. *Rare* gastric ulcer, intestinal obstruction, pancreatitis acute.

**General Disorders and Administration Site Conditions.** *Frequent* chest pain, edema, influenza-like illness. *Infrequent* chest discomfort, chills, pyrexia.

**Hepatobiliary Disorders.** *Infrequent* gall bladder disorder.

**Investigations.** *Frequent* liver function test abnormal, weight increased. *Infrequent* electrocardiogram abnormal, muscle enzyme increased, urine analysis abnormal.

**Metabolism and Nutrition Disorders.** *Infrequent* diabetes mellitus, hyperlipidemia, hypokalemia. *Rare* hypoglycemia.

**Musculoskeletal and Connective Tissue Disorders.** *Frequent* arthralgia, back pain, muscle cramp, musculoskeletal pain, myalgia. *Infrequent* arthritis, osteoporosis. *Rare* myositis.

**Nervous System Disorders.** *Frequent* disturbance in attention, dizziness, sensory disturbance. *Infrequent* amnesia, migraine, parosmia, psychomotor hyperactivity, restless legs syndrome, syncope, tremor. *Rare* balance disorder, cerebrovascular accident, convulsion, dysarthria, facial palsy, mental impairment, multiple sclerosis, nystagmus, psychomotor skills impaired, transient ischemic attack, visual field defect.

**Psychiatric Disorders.** *Infrequent* disorientation, dissociation, libido decreased, mood swings, thinking abnormal. *Rare* bradyphrenia, euphoric mood.

**Renal and Urinary Disorders.** *Frequent* polyuria. *Infrequent* nephrolithiasis, nocturia, urethral syndrome, urine abnormality. *Rare* renal failure acute, urinary retention.

**Reproductive System and Breast Disorders.** *Rare* sexual dysfunction. *Frequent* menstrual disorder. *Infrequent* erectile dysfunction.

**Respiratory, Thoracic and Mediastinal Disorders.** *Frequent* epistaxis, respiratory disorders. *Infrequent* asthma. *Rare* pleurisy, pulmonary embolism.

**Skin and Subcutaneous Tissue Disorders.** *Frequent* hyperhidrosis. *Infrequent* acne, dry skin, eczema, erythema, psoriasis, urticaria. *Rare* photosensitivity reaction.

**Vascular Disorders.** *Frequent* hot flush. *Infrequent* thrombosis.

CHANTIX has also been studied in postmarketing trials including (1) a trial conducted in patients with chronic obstructive pulmonary disease (COPD), (2) a trial conducted in generally healthy patients (similar to those in the premarketing studies) in which they were allowed to select a quit date between days 8 and 35 of treatment ("alternative quit date instruction trial"), (3) a trial conducted in patients with stable cardiovascular disease and (4) a trial conducted in patients with stable schizophrenia or schizoaffective disorder.

Adverse events in the trial of patients with COPD and in the alternative quit date instruction trial were quantitatively and qualitatively similar to those observed in premarketing studies.

In the trial of patients with stable cardiovascular disease, more types and a greater number of cardiovascular events were reported compared to premarketing studies. Treatment-emergent (on-treatment or 30 days after treatment) cardiovascular events reported with a frequency  $\geq 1\%$  in either treatment group in this study were angina pectoris (3.7% and 2.0% for varenicline and placebo, respectively), chest pain (2.5% vs. 2.3%), peripheral edema (2.0% vs. 1.1%), hypertension (1.4% vs. 2.6%), and palpitations (0.6% vs. 1.1%). Deaths and serious cardiovascular events occurring over the 52 weeks of the study (treatment emergent and non-treatment emergent) were adjudicated by a blinded, independent committee. The following treatment-emergent adjudicated events occurred with a frequency  $\geq 1\%$  in either treatment group: nonfatal MI (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalization for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularization (2.0% vs. 0.6%), hospitalization for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal

MI and hospitalization for angina. Cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

In the trial of patients with stable schizophrenia or schizoaffective disorder, 128 smokers on antipsychotic medication were randomized 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up. The most common adverse events in patients taking varenicline were nausea (24% vs. 14.0% on placebo), headache (11% vs. 19% on placebo) and vomiting (11% vs. 9% on placebo). Among reported neuropsychiatric adverse events, insomnia was the only event that occurred in either treatment group in  $\geq 5\%$  of subjects at a rate higher in the varenicline group than in placebo (10% vs. 5%). These common and neuropsychiatric adverse events occurred on treatment or within 30 days after the last dose of study drug. There was no consistent worsening of schizophrenia in either treatment group as measured by the Positive and Negative Syndrome Scale. There were no overall changes in extra-pyramidal signs, as measured by the Simpson-Angus Rating Scale. The Columbia-Suicide Severity Rating Scale was administered at baseline and at clinic visits during the treatment and non-treatment follow-up phases. Over half of the patients had a lifetime history of suicidal behavior and/or ideation (62% on varenicline vs. 51% on placebo), but at baseline, no patients in the varenicline group reported suicidal behavior and/or ideation vs. one patient in the placebo group (2%). Suicidal behavior and/or ideation were reported in 11% of the varenicline-treated and 9% of the placebo-treated patients during the treatment phase. During the post-treatment phase, suicidal behavior and/or ideation were reported in 11% of patients in the varenicline group and 5% of patients in the placebo group. Many of the patients reporting suicidal behavior and ideation in the follow-up phase had not reported such experiences in the treatment phase. However, no new suicidal ideation or behavior emerged in either treatment group shortly (within one week) after treatment discontinuation (a phenomenon noted in post-marketing reporting). There were no completed suicides. There was one suicide attempt in a varenicline-treated patient. The limited data available from this single smoking cessation study are not sufficient to allow conclusions to be drawn.

## 6.2 Postmarketing Experience

The following adverse events have been reported during post-approval use of CHANTIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide in patients attempting to quit smoking while taking CHANTIX [see **Boxed Warning, Warnings and Precautions (5.1)**]. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking.

There have been reports of hypersensitivity reactions, including angioedema [see **Warnings and Precautions (5.2)**].

There have also been reports of serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients taking CHANTIX [see **Warnings and Precautions (5.3)**].

There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischemic and hemorrhagic events in patients taking Chantix. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out.

## 7 DRUG INTERACTIONS

Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions [see *Clinical Pharmacology (12.3)*].

### 7.1 Use With Other Drugs for Smoking Cessation

Safety and efficacy of CHANTIX in combination with other smoking cessation therapies have not been studied.

**Bupropion:** Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers. The safety of the combination of bupropion and varenicline has not been established.

**Nicotine replacement therapy (NRT):** Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone. In this study, eight of twenty-two (36%) patients treated with the combination of varenicline and NRT prematurely

discontinued treatment due to adverse events, compared to 1 of 17 (6%) of patients treated with NRT and placebo.

### 7.2 Effect of Smoking Cessation on Other Drugs

Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of CHANTIX use in pregnant women. In animal studies, CHANTIX caused decreased fetal weights, increased auditory startle response, and decreased fertility in offspring. CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive and developmental toxicity studies, pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. These exposures were 36 (rats) and 50 (rabbits) times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 1 mg twice daily. While no fetal structural abnormalities occurred in either species, reduced fetal weights occurred in rabbits at the highest dose (exposures 50 times the human exposure at the MRHD based on AUC). Fetal weight reduction did not occur at animal exposures 23 times the human exposure at the MRHD based on AUC.

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. These resulted in exposures up to 36 times the human exposure (based on AUC) at the MRHD of 1 mg twice daily. Decreased fertility and increased auditory startle response occurred in offspring.

### 8.3 Nursing Mothers

It is not known whether CHANTIX is excreted in human milk. In animal studies varenicline was excreted in milk of lactating animals. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

Safety and effectiveness of CHANTIX in pediatric patients have not been established.

### 8.5 Geriatric Use

A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see *Dosage and Administration (2.2)*].

No dosage adjustment is recommended for elderly patients.

### 8.6 Renal Impairment

Varenicline is substantially eliminated by renal glomerular filtration along with active tubular secretion. Dose reduction is not required in patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance  $<30$  mL/min), and for patients with end-stage renal disease undergoing hemodialysis, dosage adjustment is needed. [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

## 9 DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

Varenicline is not a controlled substance.

### 9.3 Dependence

**Humans:** Fewer than 1 out of 1000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop.



Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction.

In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers.

**Animals** Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine; however in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

## 10 OVERDOSAGE

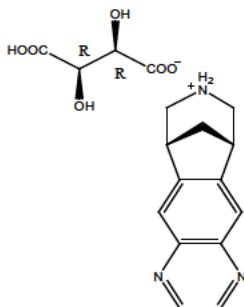
In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end stage renal disease [see *Clinical Pharmacology* (12.3)], however, there is no experience in dialysis following overdose.

## 11 DESCRIPTION

CHANTIX tablets contain varenicline (as the tartrate salt), which is a partial agonist selective for  $\alpha_4\beta_2$  nicotinic acetylcholine receptor subtypes.

Varenicline, as the tartrate salt, is a powder which is a white to off-white to slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-b][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water. Varenicline tartrate has a molecular weight of 361.35 Daltons, and a molecular formula of  $C_{13}H_{13}N_3 \cdot C_4H_6O_6$ . The chemical structure is:



CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "Pfizer" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablet debossed with "Pfizer" on one side and "CHX 1.0" on the other side. Each 0.5 mg CHANTIX tablet contains 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline free base; each 1mg CHANTIX tablet contains 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline free base. The following inactive ingredients are included in the tablets: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Varenicline binds with high affinity and selectivity at  $\alpha_4\beta_2$  neuronal nicotinic acetylcholine receptors. The efficacy of CHANTIX in smoking cessation is believed to be the result of varenicline's activity at  $\alpha_4\beta_2$  sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to these receptors.

Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to  $\alpha_4\beta_2$  neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate  $\alpha_4\beta_2$  receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to  $\alpha_4\beta_2$  receptors than to other common nicotinic receptors (>500-fold  $\alpha_3\beta_4$ , >3500-

fold  $\alpha_7$ , >20,000-fold  $\alpha_1\beta\gamma\delta$ ), or to non-nicotinic receptors and transporters (>2000-fold). Varenicline also binds with moderate affinity ( $K_i = 350$  nM) to the 5-HT<sub>3</sub> receptor.

### 12.3 Pharmacokinetics

**Absorption/Distribution** Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was ~90%. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing. Plasma protein binding of varenicline is low ( $\leq 20\%$ ) and independent of both age and renal function.

**Metabolism/Elimination** The elimination half-life of varenicline is approximately 24 hours. Varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

**Pharmacokinetics in Special Patient Populations** There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

**Renal Impairment:** Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 mL/min and  $\leq 80$  mL/min). In subjects with moderate renal impairment (estimated creatinine clearance  $\geq 30$  mL/min and  $\leq 50$  mL/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >80 mL/min). In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD) undergoing a three-hour session of hemodialysis for three days a week, varenicline exposure was increased 2.7-fold following 0.5 mg once daily administration for 12 days. The plasma  $C_{max}$  and AUC of varenicline noted in this setting were similar to those of healthy subjects receiving 1 mg twice daily. [see *Dosage and Administration* (2.2), and *Use in Specific Populations* (8.6)]. Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis [see *Overdosage* (10)].

**Geriatric Patients:** A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects.

**Pediatric Patients:** Because the safety and effectiveness of CHANTIX in pediatric patients have not been established, CHANTIX is not recommended for use in patients under 18 years of age. Single and multiple-dose pharmacokinetics of varenicline have been investigated in pediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight >55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg BID was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight  $\leq 55$  kg compared to that noted in the adult population.

**Hepatic Impairment:** Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment.

**Drug-Drug Interactions** Drug interaction studies were performed with varenicline and digoxin, warfarin, transdermal nicotine, bupropion, cimetidine, and metformin. No clinically meaningful pharmacokinetic drug-drug interactions have been identified.

*In vitro* studies demonstrated that varenicline does not inhibit the following cytochrome P450 enzymes ( $IC_{50} > 6400$  ng/mL): 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline does not induce the cytochrome P450 enzymes 1A2 and 3A4.

*In vitro* studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (e.g., metformin [see below]) are unlikely to be affected by varenicline.

*In vitro* studies demonstrated the active renal secretion of varenicline is mediated by the human organic cation transporter OCT2. Co-administration with inhibitors of OCT2 (e.g., cimetidine [see below]) may not necessitate a dose adjustment of CHANTIX as the increase in systemic exposure to CHANTIX is not expected to be clinically meaningful. Furthermore, since metabolism of varenicline represents less than 10% of its clearance, drugs known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of CHANTIX [see *Clinical Pharmacology* (12.3)]; therefore, a dose adjustment of CHANTIX would not be required.

**Metformin:** When co-administered to 30 smokers, varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of metformin (500 mg twice daily), which is a substrate of OCT2. Metformin had no effect on varenicline steady-state pharmacokinetics.

**Cimetidine:** Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) to 12 smokers increased the systemic exposure of varenicline by 29% (90% CI: 21.5%, 36.9%) due to a reduction in varenicline renal clearance.

**Digoxin:** Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose in 18 smokers.

**Warfarin:** Varenicline (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R, S)-warfarin in 24 smokers. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics [see *Drug Interactions* (7.2)].

#### **Use with Other Drugs for Smoking Cessation**

**Bupropion:** Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers [see *Drug Interactions* (7.1)].

**Nicotine replacement therapy (NRT):** Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of adverse reactions was greater for the combination than for NRT alone [see *Drug Interactions* (7.1)].

### **13 NONCLINICAL TOXICOLOGY**

#### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis** Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

**Mutagenesis** Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

**Impairment of Fertility** There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg twice daily). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg twice daily). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg twice daily).

### **14 CLINICAL STUDIES**

The efficacy of CHANTIX in smoking cessation was demonstrated in six clinical trials in which a total of 3659 chronic cigarette smokers ( $\geq 10$  cigarettes per day) were treated with CHANTIX. In all clinical studies, abstinence from smoking was determined by patient self-report and verified by measurement of exhaled carbon monoxide ( $\text{CO} \leq 10$  ppm) at weekly visits. Among the CHANTIX-treated patients enrolled in these studies, the completion rate was 65%. Except for the dose-ranging study (Study 1) and the maintenance of abstinence study (Study 6), patients were treated for 12 weeks and then were followed for 40 weeks post-treatment. Most patients enrolled in these trials were white (79-96%). All studies enrolled almost equal numbers of men and women. The average age of patients in these studies was 43 years. Patients on average had smoked about 21 cigarettes per day for an average of approximately 25 years. Patients set a date to stop smoking (target quit date) with dosing starting 1 week before this date.

Three additional studies were conducted in patients with cardiovascular disease, in patients with chronic obstructive pulmonary disease [see *Clinical Studies* (14.4)], and in patients instructed to select their quit date within days 8 and 35 of treatment [see *Clinical Studies* (14.5)].

In all studies, patients were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation

counseling at each weekly treatment visit according to Agency for Healthcare Research and Quality guidelines.

#### **14.1 Initiation of Abstinence**

**Study 1** This was a six-week dose-ranging study comparing CHANTIX to placebo. This study provided initial evidence that CHANTIX at a total dose of 1 mg per day or 2 mg per day was effective as an aid to smoking cessation.

**Study 2** This study of 627 patients compared CHANTIX 1 mg per day and 2 mg per day with placebo. Patients were treated for 12 weeks (including one week titration) and then were followed for 40 weeks post-treatment. CHANTIX was given in two divided doses daily. Each dose of CHANTIX was given in two different regimens, with and without initial dose titration, to explore the effect of different dosing regimens on tolerability. For the titrated groups, dosage was titrated up over the course of one week, with full dosage achieved starting with the second week of dosing. The titrated and nontitrated groups were pooled for efficacy analysis.

Forty-five percent of patients receiving CHANTIX 1 mg per day (0.5 mg twice daily) and 51% of patients receiving 2 mg per day (1 mg twice daily) had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% of patients in the placebo group (Figure 1). In addition, 31% of the 1 mg per day group and 31% of the 2 mg per day group were continuously abstinent from one week after TQD through the end of treatment as compared to 8% of the placebo group.

**Study 3** This flexible-dosing study of 312 patients examined the effect of a patient-directed dosing strategy of CHANTIX or placebo. After an initial one-week titration to a dose of 0.5 mg twice daily, patients could adjust their dosage as often as they wished between 0.5 mg once daily to 1 mg twice daily per day. Sixty-nine percent of patients titrated to the maximum allowable dose at any time during the study. For 44% of patients, the modal dose selected was 1 mg twice daily; for slightly over half of the study participants, the modal dose selected was 1 mg/day or less.

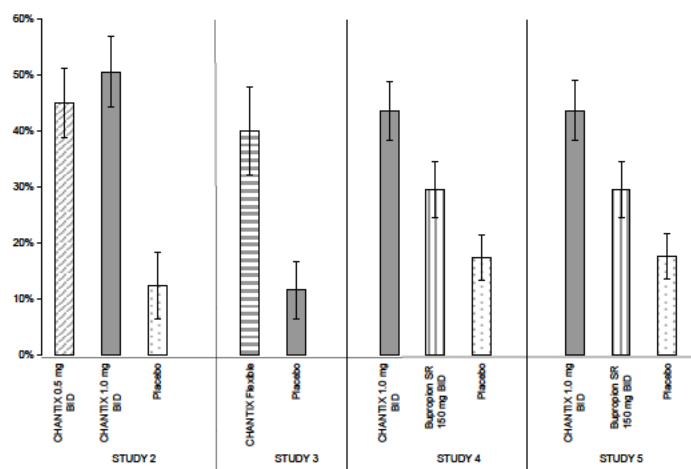
Of the patients treated with CHANTIX, 40% had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% in the placebo group. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 9% of the placebo group.

**Study 4 and Study 5** These identical double-blind studies compared CHANTIX 2 mg per day, bupropion sustained-release (SR) 150 mg twice daily, and placebo. Patients were treated for 12 weeks and then were followed for 40 weeks post-treatment. The CHANTIX dosage of 1 mg twice daily was achieved using a titration of 0.5 mg once daily for the initial 3 days followed by 0.5 mg twice daily for the next 4 days. The bupropion SR dosage of 150 mg twice daily was achieved using a 3-day titration of 150 mg once daily. Study 4 enrolled 1022 patients and Study 5 enrolled 1023 patients. Patients inappropriate for bupropion treatment or patients who had previously used bupropion were excluded.

In Study 4, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (17%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 12% of the placebo group and 23% of the bupropion SR group.

Similarly in Study 5, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (18%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 11% of the placebo group and 21% of the bupropion SR group.

**Figure 1: Continuous Abstinence, Weeks 9 through 12**



**Table 64: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)**

	CHANTIX 0.5 mg BID	CHANTIX 1 mg BID	CHANTIX Flexible	Bupropion SR	Placebo
Study 2	45% (39%, 51%)	51% (44%, 57%)			12% (6%, 18%)
Study 3			40% (32%, 48%)		12% (7%, 17%)
Study 4		44% (38%, 49%)		30% (25%, 35%)	17% (13%, 22%)
Study 5		44% (38%, 49%)		30% (25%, 35%)	18% (14%, 22%)

BID = twice daily

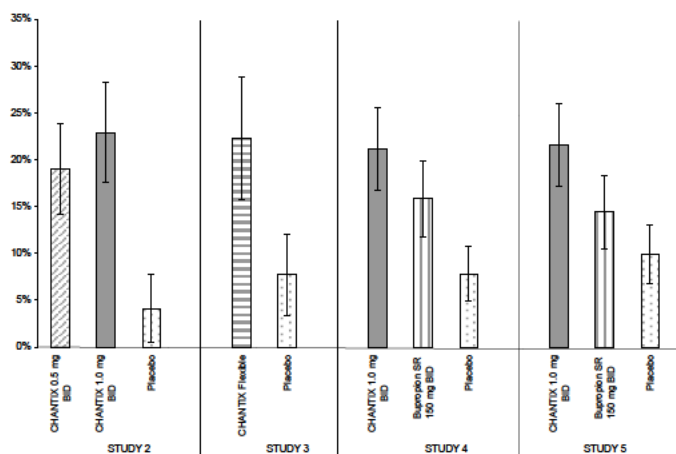
#### 14.2 Urge to Smoke

Based on responses to the Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal scale "urge to smoke" item, CHANTIX reduced urge to smoke compared to placebo.

#### 14.3 Long-Term Abstinence

Studies 1 through 5 included 40 weeks of post-treatment follow-up. In each study, CHANTIX-treated patients were more likely to maintain abstinence throughout the follow-up period than were patients treated with placebo (Figure 2, Table 75).

**Figure 2: Continuous Abstinence, Weeks 9 through 52**



**Table 75: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) across different studies**

	CHANTIX 0.5 mg BID	CHANTIX 1 mg BID	CHANTIX Flexible	Bupropion SR	Placebo
Study 2	19% (14%, 24%)	23% (18%, 28%)			4% (1%, 8%)
Study 3			22% (16%, 29%)		8% (3%, 12%)
Study 4		21% (17%, 26%)		16% (12%, 20%)	8% (5%, 11%)
Study 5		22% (17%, 26%)		14% (11%, 18%)	10% (7%, 13%)

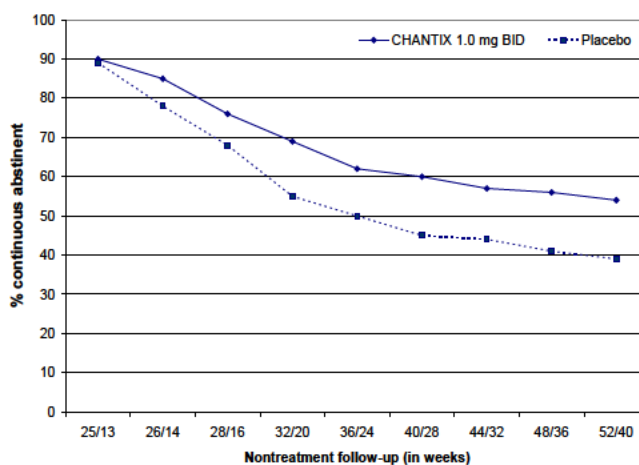
BID = twice daily

**Study 6** This study assessed the effect of an additional 12 weeks of CHANTIX therapy on the likelihood of long-term abstinence. Patients in this study (n=1927) were treated with open-label CHANTIX 1 mg twice daily for 12 weeks. Patients who had stopped smoking for at least a week by Week 12 (n=1210) were then randomized to double-blind treatment with CHANTIX (1 mg twice daily) or placebo for an additional 12 weeks and then followed for 28 weeks post-treatment.

The continuous abstinence rate from Week 13 through Week 24 was higher for patients continuing treatment with CHANTIX (70%) than for patients switching to placebo (50%). Superiority to placebo was also maintained during 28 weeks post-treatment follow-up (CHANTIX 54% versus placebo 39%).

In Figure 3 below, the x-axis represents the study week for each observation, allowing a comparison of groups at similar times after discontinuation of CHANTIX; post-CHANTIX follow-up begins at Week 13 for the placebo group and Week 25 for the CHANTIX group. The y-axis represents the percentage of patients who had been abstinent for the last week of CHANTIX treatment and remained abstinent at the given timepoint.

**Figure 3: Continuous Abstinence Rate during Nontreatment Follow-Up**



#### 14.4 Subjects with Cardiovascular and Chronic Obstructive Pulmonary Disease

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged 35 to 75 years with stable, documented cardiovascular disease (diagnoses other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomized to CHANTIX 1 mg twice daily (n=353) or placebo (n=350) for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47%) compared to subjects treated with placebo (14%) and from week 9 through 52 (20%) compared to subjects treated with placebo (7%).

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged ≥ 35 years with mild-to-moderate COPD with post-bronchodilator FEV<sub>1</sub>/FVC <70% and FEV<sub>1</sub> ≥ 50% of predicted normal value. Subjects were randomized to CHANTIX 1 mg twice daily (N=223) or placebo (N=237) for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (41%) compared to subjects treated with placebo (9%) and from week 9 through 52 (19%) compared to subjects treated with placebo (6%).

**Table 86: Continuous Abstinence (95% confidence interval), Studies in Patients with Cardiovascular Disease (CVD) and Chronic Obstructive Pulmonary Disease (COPD)**

	Weeks 9 through 12		Weeks 9 through 52	
	CHANTIX 1 mg BID	Placebo	CHANTIX 1 mg BID	Placebo
CVD Study	47% (42%, 53%)	14% (11%, 18%)	20% (16%, 24%)	7% (5%, 10%)
COPD Study	41% (34%, 47%)	9% (6%, 13%)	19% (14%, 24%)	6% (3%, 9%)

BID = twice daily

#### 14.5 Alternative Instructions for Setting a Quit Date

CHANTIX was evaluated in a double-blind, placebo-controlled trial where patients were instructed to select a target quit date between Day 8 and Day 35 of treatment. Subjects were randomized 3:1 to CHANTIX 1 mg twice daily (N=486) or placebo (N=165) for 12 weeks of treatment and followed for



another 12 weeks post-treatment. Patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (54%) compared to patients treated with placebo (19%) and from weeks 9 through 24 (35%) compared to subjects treated with placebo (13%).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "Pfizer" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablet debossed with "Pfizer" on one side and "CHX 1.0" on the other side. CHANTIX is supplied in the following package configurations:

	Description	NDC
Packs	Starting Month PAK (First month of therapy): Pack includes 1 card of 0.5 mg x 11 tablets and 3 cards of 1 mg x 14 tablets	NDC 0069-0471-97
	Continuing Month PAK (Continuing months of therapy): Pack includes 4 cards of 1 mg x 14 tablets	NDC 0069-0469-97
	Starting Month Box: 0.5 mg x 11 tablets and 1 mg x 42 tablets	NDC 0069-0471-02
	Continuing Month Box : 1 mg x 56 tablets	NDC 0069-0469-12
Bottles	0.5 mg - bottle of 56	NDC 0069-0468-56
	1 mg - bottle of 56	NDC 0069-0469-56

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) (see USP Controlled Room Temperature).

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

### 17.1 Initiate Treatment and Continue to Attempt to Quit if Lapse

Instruct patients to set a date to quit smoking and to initiate CHANTIX treatment one week before the quit date. Alternatively, the patient can begin CHANTIX dosing and then set a date to quit smoking between days 8 and 35 of treatment. Encourage patients to continue to attempt to quit if they have early lapses after quit day [see Dosage and Administration (2.1)].

### 17.2 How To Take

Advise patients that CHANTIX should be taken after eating, and with a full glass of water [see Dosage and Administration (2.1)].

### 17.3 Starting Week Dosage

Instruct patients on how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. Explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening [see Dosage and Administration (2.1)].

### 17.4 Continuing Weeks Dosage

Advise patients that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening [see Dosage and Administration (2.1)].

### 17.5 Dosage Adjustment for CHANTIX or Other Drugs

Inform patients that nausea and insomnia are side effects of CHANTIX and are usually transient; however, advise patients that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.

Inform patients that some drugs may require dose adjustment after quitting smoking [see Dosage and Administration (2.1)].

## 17.6 Counseling and Support

Provide patients with educational materials and necessary counseling to support an attempt at quitting smoking [see Dosage and Administration (2.1)].

## 17.7 Neuropsychiatric Symptoms

Inform patients that some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation and suicide when attempting to quit smoking while taking CHANTIX. If patients develop agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to discontinue CHANTIX and report these symptoms to their healthcare provider immediately [see **Boxed Warning**, Warnings and Precautions (5.1), Adverse Reactions (6.2)].

## 17.8 History of Psychiatric Illness

Encourage patients to reveal any history of psychiatric illness prior to initiating treatment.

## 17.9 Nicotine Withdrawal

Inform patients that quitting smoking, with or without CHANTIX, may be associated with nicotine withdrawal symptoms (including depression or agitation) or exacerbation of pre-existing psychiatric illness.

## 17.10 Angioedema

Inform patients that there have been reports of angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue CHANTIX and immediately seek medical care if they experience these symptoms [see Warnings and Precautions (5.2), and Adverse Reactions (6.2)].

## 17.11 Serious Skin Reactions

Inform patients that serious skin reactions, such as Stevens-Johnson Syndrome and erythema multiforme, were reported by some patients taking CHANTIX. Advise patients to stop taking CHANTIX at the first sign of rash with mucosal lesions or skin reaction and contact a healthcare provider immediately [see Warnings and Precautions (5.3), and Adverse Reactions (6.2)].

## 17.12 Cardiovascular Events

Patients should be instructed to notify their health-care providers of symptoms of new or worsening cardiovascular events and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke. [see Warnings and Precautions (5.4), and Adverse Reactions (6.1)].

## 17.13 Driving or Operating Machinery

Advise patients to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them [see Warnings and Precautions (5.5)].

## 17.14 Vivid, Unusual, or Strange Dreams

Inform patients that they may experience vivid, unusual or strange dreams during treatment with CHANTIX.

## 17.15 Pregnancy and Lactation

Patients who are pregnant or breastfeeding or planning to become pregnant should be advised of: the risks of smoking to a pregnant mother and her developing baby, the potential risks of CHANTIX use during pregnancy and breastfeeding, and the benefits of smoking cessation with and without CHANTIX [see Use in Specific Populations (8.1 and 8.3)].

This product's label may have been updated. For full prescribing information, please visit [www.pfizer.com](http://www.pfizer.com)



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**MEDICATION GUIDE**  
**CHANTIX® (CHANT-i-ks)**  
**(varenicline) Tablets**

Read the Medication Guide that comes with CHANTIX before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your condition or treatment.

**What is the most important information I should know about CHANTIX?**

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Some people have had changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions while using CHANTIX to help them quit smoking. Some people had these symptoms when they began taking CHANTIX, and others developed them after several weeks of treatment, or after stopping CHANTIX.

If you, your family, or caregiver notice agitation, hostility, depression or changes in behavior or thinking that are not typical for you, or you develop any of the following symptoms, stop taking CHANTIX and call your doctor right away:

- thoughts about suicide or dying, or attempts to commit suicide
- new or worse depression, anxiety, or panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused
- other unusual changes in behavior or mood

When you try to quit smoking, with or without CHANTIX, you may have symptoms that may be due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

Before taking CHANTIX, tell your doctor if you have ever had depression or other mental health problems. You should also tell your doctor about any symptoms you had during other times you tried to quit smoking, with or without CHANTIX.

See **“What are the possible side effects of CHANTIX?”**

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Some people can have allergic reactions to CHANTIX. Some of these allergic reactions can be life-threatening and include: swelling of the face, mouth (tongue, lips), and throat that can cause trouble breathing. If you have these symptoms, stop taking CHANTIX and get medical attention right away.

Some people can have serious skin reactions while taking CHANTIX. These can include rash, swelling, redness, and peeling of the skin. Some of these reactions can become life-threatening. If you have a rash with peeling skin or blisters in your mouth, stop taking CHANTIX and see your doctor right away.

**What is CHANTIX?**

CHANTIX is a prescription medicine to help adults stop smoking.



Quitting smoking can lower your chances of having lung disease, heart disease or getting certain types of cancer that are related to smoking.

CHANTIX is not recommended for people under 18 years of age.

CHANTIX has not been studied with other treatments for stopping smoking.

### **Who should not take CHANTIX?**

Do not take CHANTIX if you have had a serious allergic or skin reaction to CHANTIX, which may include:

- swelling of the face, mouth, and throat that can cause trouble breathing.
- rash, swelling, redness, and peeling of the skin.

### **What should I tell my doctor before taking CHANTIX?**

Before you take CHANTIX, tell your doctor if you:

- have ever had depression or other mental health problems. See “What is the most important information I should know about CHANTIX?”
- have kidney problems or get kidney dialysis. Your doctor may prescribe a lower dose of CHANTIX for you.
- have heart or blood vessel problems
- have any allergies. See the end of this Medication Guide for a complete list of ingredients in CHANTIX.
- have any other medical conditions
- are pregnant or plan to become pregnant. Ask your doctor for help to stop smoking before you get pregnant because smoking during pregnancy puts you and your baby at risk for problems during pregnancy. CHANTIX has not been studied in pregnant women. It is not known if CHANTIX will harm your unborn baby.
- are breastfeeding. CHANTIX has not been studied in breastfeeding women. It is not known if CHANTIX passes into breast milk. You and your doctor should talk about the best way to feed your baby if you take CHANTIX.

Tell your doctor about all your other medicines, including prescription and nonprescription medicines, vitamins and herbal supplements. Especially, tell your doctor if you take:

- insulin
- asthma medicines
- blood thinners

### **When you stop smoking, there may be a change in how these and other medicines work for you.**

You should not use CHANTIX while using other medicines to quit smoking. Tell your doctor if you use other treatments to quit smoking.

Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist when you get a new medicine.

### **How should I take CHANTIX?**

- There are 2 ways that you can use CHANTIX to help you quit smoking. Talk to your doctor about the following 2 ways to use CHANTIX:
  1. Choose a **quit date** when you will stop smoking. Start taking CHANTIX 1 week (7 days) before your **quit date**. This lets CHANTIX build up in your body. You can keep smoking during this time. Make sure that you try to stop smoking on your **quit date**. If you slip-up and smoke, try again. Some people need to take CHANTIX for a few weeks for CHANTIX to work best.

OR

2. You can also start taking CHANTIX before you choose a **quit date**. Pick a date to quit smoking that is between days 8 and 35 of treatment. Make sure that you try to stop smoking on your **quit date**. If you slip-up and smoke, try again. Some people need to take CHANTIX for a few weeks for CHANTIX to work best.
- Take CHANTIX exactly as prescribed by your doctor.
    1. Take CHANTIX after eating and with a full glass (8 ounces) of water.
    2. Most people will take CHANTIX for up to 12 weeks. If you have completely quit smoking by 12 weeks, your doctor may prescribe CHANTIX for another 12 weeks to help you stay cigarette-free.
  - CHANTIX comes as a white tablet (0.5 mg) and a blue tablet (1 mg). You start with the white tablet and then usually go to the blue tablet. See the chart below for dosing instructions.

<u>Day 1 to Day 3</u>	<ul style="list-style-type: none"> <li>• <u>White</u> tablet (0.5 mg)</li> <li>• Take 1 tablet each day</li> </ul>
<u>Day 4 to Day 7</u>	<ul style="list-style-type: none"> <li>• <u>White</u> tablet (0.5 mg)</li> <li>• Take 1 in the morning and 1 in the evening</li> </ul>
<u>Day 8 to end of treatment</u>	<ul style="list-style-type: none"> <li>• <u>Blue</u> tablet (1 mg)</li> <li>• Take 1 in the morning and 1 in the evening</li> </ul>

- This dosing schedule may not be right for everyone. Talk to your doctor if you are having side effects such as nausea, strange dreams, or sleep problems. Your doctor may want to reduce your dose.
- If you miss a dose of CHANTIX, take it as soon as you remember. If it is close to the time for your next dose, wait. Just take your next dose at your regular dose.

#### **What should I avoid while taking CHANTIX?**

Use caution driving or operating machinery until you know how CHANTIX may affect you. Some people who use CHANTIX may feel sleepy, dizzy, or have trouble concentrating, that can make it hard to drive or perform other activities safely.

#### **What are the possible side effects of CHANTIX?**

##### **Serious side effects of CHANTIX may include:**

- **New or worse mental health problems**, which have been reported in some people. See “What is the most important information I should know about CHANTIX?”
- **New or worse heart or blood vessel (cardiovascular) problems**, mostly in people, who already have cardiovascular problems. Tell your doctor if you have any changes in symptoms during treatment with CHANTIX.

##### **Get emergency medical help right away if you have any of the following symptoms of a heart attack, including:**

- chest discomfort (uncomfortable pressure, squeezing, fullness or pain) that lasts more than a few minutes, or that goes away and comes back
- pain or discomfort in one or both arms, back, neck, jaw or stomach
- shortness of breath, sweating, nausea, vomiting, or feeling lightheaded associated with chest discomfort
- The most common side effects of CHANTIX include:
  - nausea
  - sleep problems (trouble sleeping or vivid, unusual, or strange dreams)
  - constipation
  - gas

- vomiting

Tell your doctor about side effects that bother you or that do not go away.

These are not all the side effects of CHANTIX. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store CHANTIX?**

- Store CHANTIX at room temperature, 59 to 86°F (15 to 30°C).
- Safely dispose of CHANTIX that is out of date or no longer needed.
- **Keep CHANTIX and all medicines out of the reach of children.**

#### **General information about CHANTIX**

**Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CHANTIX for a condition for which it was not prescribed. Do not give your CHANTIX to other people, even if they have the same symptoms that you have. It may harm them.**

This Medication Guide summarizes the most important information about CHANTIX. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CHANTIX that is written for healthcare professionals.

For more about CHANTIX and tips on how to quit smoking, go to [www.CHANTIX.com](http://www.CHANTIX.com) or call 1-877-CHANTIX (877-242-6849).

#### **What are the ingredients in CHANTIX?**

**Active ingredient:** varenicline tartrate

**Inactive ingredients:** microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry ® White (for 0.5 mg), Opadry ® Blue (for 1 mg), and Opadry® Clear (for both 0.5 mg and 1 mg)



LAB-0328-11.0

Revised December 2012

This Medication Guide has been approved by the U.S. Food and Drug Administration.

LAB-0328-11.10

Revised [September 2014](#)~~[October 2013](#)~~~~[December 2012](#)~~

[LAB-0328-11.X4](#)

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CHANTIX safely and effectively. See full prescribing information for CHANTIX.

CHANTIX® (varenicline) Tablets

Initial U.S. Approval: 2006

### WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

See full prescribing information for complete boxed warning.

- Serious neuropsychiatric events have been reported in patients taking CHANTIX. (5.1 and 6.2)
- Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior while taking CHANTIX or shortly after discontinuing CHANTIX. (5.1 and 6.2)
- Weigh the risks of CHANTIX against benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (5.1 and 6.2)

### RECENT MAJOR CHANGES

Warnings and Precautions

Neuropsychiatric Symptoms and Suicidality (5.1)

09/2014

Seizures (5.2)

09/2014

Interaction with Alcohol (5.3)

09/2014

### INDICATIONS AND USAGE

CHANTIX is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment. (1 and 2.1)

### DOSAGE AND ADMINISTRATION

- Begin CHANTIX dosing one week before the date set by the patient to stop smoking. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment. (2.1)
- Starting week: 0.5 mg once daily on days 1-3 and 0.5 mg twice daily on days 4-7. (2.1)
- Continuing weeks: 1 mg twice daily for a total of 12 weeks. (2.1)
- An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence. (2.1)
- Renal impairment: Reduce the dose in patients with severe renal impairment (estimated creatinine clearance <30 mL/min). (2.2)
- Consider dose reduction for patients who cannot tolerate adverse effects. (2.1)
- Another attempt at treatment is recommended for those who fail to stop smoking or relapse when factors contributing to the failed attempt have been addressed. (2.1)
- Provide patients with appropriate educational materials and counseling to support the quit attempt. (2.1)

### DOSAGE FORMS AND STRENGTHS

Tablets: 0.5 mg and 1 mg (3)

### CONTRAINDICATIONS

History of serious hypersensitivity or skin reactions to CHANTIX (4)

### WARNINGS AND PRECAUTIONS

- **Seizures:** New or worsening seizures have been observed in patients taking CHANTIX. CHANTIX should be used cautiously in patients with a history of seizures or other factors that can lower the seizure threshold. (5.2)
- **Interaction with Alcohol:** Increased effects of alcohol have been reported. Instruct patients to reduce the amount of alcohol they consume until they know whether CHANTIX affects them. (5.3)
- **Accidental injury:** Accidental injuries (e.g., traffic accidents) have been reported. Instruct patients to use caution driving or operating machinery until they know how CHANTIX may affect them. (5.4)
- **Cardiovascular events:** A meta-analysis of 15 clinical trials, including a trial in patients with stable cardiovascular disease, demonstrated that while cardiovascular events were infrequent overall, some were reported more frequently in patients treated with CHANTIX. These events occurred primarily in patients with known cardiovascular disease. In both the clinical trial and meta-analysis, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX. Instruct patients to notify their health care providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke. (5.5 and 6.1)
- **Angioedema and hypersensitivity reactions:** Such reactions, including angioedema, infrequently life threatening, have been reported. Instruct patients to discontinue CHANTIX and immediately seek medical care if symptoms occur. (5.6 and 6.2)
- **Serious skin reactions:** Rare, potentially life-threatening skin reactions have been reported. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions. (5.7 and 6.2)
- **Nausea:** Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (5.8)

### ADVERSE REACTIONS

Most common adverse reactions (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Other smoking cessation therapies: Safety and efficacy in combination with other smoking cessation therapies has not been established. Coadministration of varenicline and transdermal nicotine resulted in a high rate of discontinuation due to adverse events. (7.1)
- Effect of smoking cessation: Pharmacokinetics or pharmacodynamics of certain drugs may be altered due to smoking cessation with CHANTIX, necessitating dose adjustment. (7.2)

### USE IN SPECIFIC POPULATIONS

- **Pregnancy:** CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- **Nursing Mothers:** Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
- **Pediatric Use:** Safety and effectiveness not established (8.4)
- **Renal Impairment:** Dosage adjustment is required for severe renal impairment. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2014

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## FULL PRESCRIBING INFORMATION

### WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

Serious neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. [see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]

## 1 INDICATIONS AND USAGE

CHANTIX is indicated for use as an aid to smoking cessation treatment.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Usual Dosage for Adults

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Provide patients with appropriate educational materials and counseling to support the quit attempt.

The patient should set a date to stop smoking. Begin CHANTIX dosing one week before this date. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment.

CHANTIX should be taken after eating and with a full glass of water.

The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – end of treatment:	1 mg twice daily

Patients should be treated with CHANTIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks' treatment with CHANTIX is recommended to further increase the likelihood of long-term abstinence.

Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

Consider a temporary or permanent dose reduction in patients who cannot tolerate the adverse effects of CHANTIX.

### 2.2 Dosage in Special Populations

**Patients with Impaired Renal Function** No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance <30 mL/min), the recommended starting dose of CHANTIX is 0.5 mg once daily. The dose may then be titrated as needed to a maximum dose of 0.5 mg twice a day. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

**Elderly and Patients with Impaired Hepatic Function** No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see Use in Specific Populations (8.5)].

## 3 DOSAGE FORMS AND STRENGTHS

Capsular, biconvex tablets: 0.5 mg (white to off-white, debossed with "Pfizer" on one side and "CHX 0.5" on the other side) and 1 mg (light blue, debossed with "Pfizer" on one side and "CHX 1.0" on the other side).

## 4 CONTRAINDICATIONS

CHANTIX is contraindicated in patients with a known history of serious hypersensitivity reactions or skin reactions to CHANTIX.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Neuropsychiatric Symptoms and Suicidality

Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX [see Boxed Warning and Adverse Reactions (6.2)]. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to

smoke. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX. Limited safety data are available from post-marketing smoking cessation studies in two patient groups: 1) patients with major depressive disorder, and 2) patients with stable schizophrenia or schizoaffective disorder [see *Adverse Reactions* (6.1)].

Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior directed to oneself or others, may have been worsened by concomitant use of alcohol [see *Interaction with Alcohol* (5.3), *Adverse Reactions* (6.2)].

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, depressed mood, changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

Since the initial signal of neuropsychiatric symptoms and suicidality emerged, additional analyses and studies have been conducted to further evaluate this association.

#### Analyses of clinical trials

A meta-analysis of 5 randomized, double blind, placebo controlled trials, including 1907 patients (1130 CHANTIX, 777 placebo) was conducted to assess suicidal ideation and behavior as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). This meta-analysis included one trial (N=127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (N=525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behavior in patients treated with CHANTIX compared to patients treated with placebo, with a Risk Ratio (RR) of 0.79 (95% Confidence Interval [CI]: 0.46, 1.36), as shown in Table 1. Forty-eight (48) of the 55 patients who reported suicidal ideation or behavior (24 CHANTIX, 24 placebo) were observed in the two trials that enrolled patients with a history of schizophrenia, schizoaffective disorder, or depression. Few events were observed in the other three trials (4 CHANTIX, 3 placebo).

**Table 1. Number of patients and Risk Ratio for Suicidal Ideation and/or Behavior Reported on C-SSRS from a Meta-Analysis of 5 Clinical Trials Comparing CHANTIX to Placebo**

	CHANTIX (N=1130)	Placebo (N=777)
Patients with Suicidal ideation and/or behavior* [n (%)]**	28 (2.5)	27 (3.5)
Patient-years of exposure	325	217
Risk Ratio # (RR; 95% CI)	0.79 (0.46, 1.36)	

\* Of the events, one patient in each treatment arm reported suicidal behavior

\*\* Patients with events up to 30 days after treatment; % are not weighted by study

# RR of incidence rates per 100 patient years

A pooled analysis of 18 double-blind, randomized, placebo-controlled clinical trials, which includes the 5 trials that collected C-SSRS described in Table 1, was conducted to assess the psychiatric safety of CHANTIX. This pooled analysis included 8521 patients (5072 CHANTIX, 3449 placebo), some of whom had psychiatric conditions at baseline. Table 2 describes the most frequently ( $\geq 1\%$ ) reported adverse events related to psychiatric safety. The results showed a similar incidence of common psychiatric events in patients treated with CHANTIX compared to patients treated with placebo.

**Table 2. Psychiatric Adverse Events Occurring in  $\geq 1\%$  of Patients from Pooled Analysis of 18 Clinical Trials**

	CHANTIX (N=5072)	Placebo (N=3449)
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)
Depressed mood disorders and disturbances	179 (3.5)	108 (3.1)
Mood disorders and disturbances NEC*	116 (2.3)	53 (1.5)

\* NEC = Not Elsewhere Classified

Counts (percentages) corresponds to the number of patients reporting the event

#### Observational Studies

Four observational studies, each including 10,000 to 30,000 users of CHANTIX in the adjusted analyses, compared the risk of selected serious neuropsychiatric events (neuropsychiatric hospitalizations, fatal and non-fatal self-harm), between CHANTIX users and prescription NRT or bupropion users. All studies were retrospective cohort studies and included patients with and without a psychiatric history.

Two of the studies found no difference in risk of neuropsychiatric hospitalizations between CHANTIX users and nicotine patch users (Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI]: 0.56–2.34 in the first study, and 0.76; 95% CI: 0.40–1.46 in the second study). However, neither study validated the diagnostic codes used to identify outcomes against medical records. A third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between CHANTIX users and bupropion users (HR 0.85; 95% CI: 0.55–1.30). Bupropion has also been associated with neuropsychiatric adverse events. A fourth study examined risk of fatal and non-fatal self-harm in users of CHANTIX compared to users of NRT. Although the occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 CHANTIX users and six cases in 81,545 NRT users), this study has important limitations. Most importantly, these data were captured following public awareness of reports of neuropsychiatric adverse events in CHANTIX users. CHANTIX users had fewer comorbid conditions that could put them at risk for neuropsychiatric adverse events, suggesting that patients with a history of neuropsychiatric illness were preferentially prescribed NRT, and healthier patients were preferentially prescribed CHANTIX.

Outcomes examined in these studies did not include the full range of neuropsychiatric adverse events that have been reported.

#### 5.2 Seizures

During clinical trials and the post-marketing experience, there have been reports of seizures in patients treated with CHANTIX. Some patients had no history of seizures, whereas others had a history of seizure disorder that was remote or well-controlled. In most cases, the seizure occurred within the first month of therapy. Weigh this potential risk against the potential benefits before prescribing CHANTIX in patients with a history of seizures or other factors that can lower the seizure threshold. Advise patients to discontinue CHANTIX and contact a healthcare provider immediately if they experience a seizure while on treatment [see *Adverse Reactions* (6.2)].

#### 5.3 Interaction with Alcohol

There have been post-marketing reports of patients experiencing increased intoxicating effects of alcohol while taking CHANTIX. Some cases described unusual and sometimes aggressive behavior, and were often accompanied by amnesia for the events. Advise patients to reduce the amount of alcohol they consume while taking CHANTIX until they know whether CHANTIX affects their tolerance for alcohol [see *Adverse Reactions* (6.2)].

#### 5.4 Accidental Injury

There have been postmarketing reports of traffic accidents, near-miss incidents in traffic, or other accidental injuries in patients taking CHANTIX. In some cases, the patients reported somnolence, dizziness, loss of consciousness or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. Advise patients to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

#### 5.5 Cardiovascular Events

In a placebo-controlled clinical trial of CHANTIX administered to patients with stable cardiovascular disease, with approximately 350 patients per treatment arm, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX, but certain nonfatal cardiovascular events occurred more frequently in patients treated with CHANTIX than in patients treated with placebo [see *Clinical Trials Experience* (6.1)]. Table 3 below shows the incidence of deaths and of selected nonfatal serious cardiovascular events occurring more frequently in the CHANTIX arm compared to the placebo arm. These events were adjudicated by an independent blinded committee. Nonfatal

serious cardiovascular events not listed occurred at the same incidence or more commonly in the placebo arm. Patients with more than one cardiovascular event of the same type are counted only once per row. Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina.

**Table 3. Mortality and Adjudicated Nonfatal Serious Cardiovascular Events in the Placebo-Controlled CHANTIX Trial in Patients with Stable Cardiovascular Disease**

Mortality and Cardiovascular Events	CHANTIX (N=353) n (%)	Placebo (N=350) n (%)
<b>Mortality (Cardiovascular &amp; All-cause up to 52 wks)</b>		
Cardiovascular death	1 (0.3)	2 (0.6)
All-cause mortality	2 (0.6)	5 (1.4)
<b>Nonfatal Cardiovascular Events (rate on CHANTIX &gt; Placebo)</b>		
<u>Up to 30 days after treatment</u>		
Nonfatal myocardial infarction	4 (1.1)	1 (0.3)
Nonfatal Stroke	2 (0.6)	0 (0)
<u>Beyond 30 days after treatment &amp; up to 52 weeks</u>		
Nonfatal myocardial infarction	3 (0.8)	2 (0.6)
Need for coronary revascularization	7 (2.0)	2 (0.6)
Hospitalization for angina pectoris	6 (1.7)	4 (1.1)
Transient ischemia attack	1 (0.3)	0 (0)
New diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure	5 (1.4)	2 (0.6)

A meta-analysis of 15 clinical trials of  $\geq 12$  weeks treatment duration, including 7002 patients (4190 CHANTIX, 2812 placebo), was conducted to systematically assess the cardiovascular safety of CHANTIX. The study in patients with stable cardiovascular disease described above was included in the meta-analysis. There were lower rates of all-cause mortality (CHANTIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHANTIX 2 [0.05%]; placebo 2 [0.07%]) in the CHANTIX arms compared with the placebo arms in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred in the trials included in the meta-analysis, as described in Table 4. These events occurred primarily in patients with known cardiovascular disease.

**Table 4. Number of MACE cases, Hazard Ratio and Rate Difference in a Meta-Analysis of 15 Clinical Trials Comparing CHANTIX to Placebo\***

	CHANTIX N=4190	Placebo N=2812
<b>MACE cases, n (%)</b>	13 (0.31%)	6 (0.21%)
Patient-years of exposure	1316	839
<b>Hazard Ratio (95% CI)</b>		
	1.95 (0.79, 4.82)	
<b>Rate Difference per 1,000 patient-years (95% CI)</b>		
	6.30 (-2.40, 15.10)	

\*Includes MACE occurring up to 30 days post treatment.

The meta-analysis showed that exposure to CHANTIX resulted in a hazard ratio for MACE of 1.95 (95% confidence interval from 0.79 to 4.82) for patients up to 30 days after treatment; this is equivalent to an estimated increase of 6.3 MACE events per 1,000 patient-years of exposure. The meta-analysis showed higher rates of CV endpoints in patients on CHANTIX relative to placebo across different time frames and pre-specified sensitivity analyses, including various study groupings and CV outcomes. Although these findings were not statistically significant they were consistent. Because the number of events was small overall, the power for finding a statistically significant difference in a signal of this magnitude is low.

CHANTIX was not studied in patients with unstable cardiovascular disease or cardiovascular events occurring within two months before screening. Patients should be advised to notify a health care provider of new or worsening symptoms of cardiovascular disease. The risks of CHANTIX should be weighed against the benefits of its use in smokers with cardiovascular disease. Smoking

is an independent and major risk factor for cardiovascular disease. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo.

## 5.6 Angioedema and Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions including angioedema in patients treated with CHANTIX [see *Adverse Reactions* (6.2), and *Patient Counseling Information* (17.10)]. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). There were infrequent reports of life-threatening angioedema requiring emergent medical attention due to respiratory compromise. Instruct patients to discontinue CHANTIX and immediately seek medical care if they experience these symptoms

## 5.7 Serious Skin Reactions

There have been postmarketing reports of rare but serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients using CHANTIX [see *Adverse Reactions* (6.2)]. As these skin reactions can be life-threatening, instruct patients to stop taking CHANTIX and contact a healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.

## 5.8 Nausea

Nausea was the most common adverse reaction reported with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some patients, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. For patients treated to the maximum recommended dose of 1 mg twice daily following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking CHANTIX 0.5 mg twice daily following initial titration, the incidence was 16% compared with 11% for placebo. Approximately 3% of patients treated with CHANTIX 1 mg twice daily in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, a dose reduction should be considered.

## 6 ADVERSE REACTIONS

The following serious adverse reactions were reported in postmarketing experience and are discussed in greater detail in other sections of the labeling:

- Neuropsychiatric symptoms and suicidality [see *Boxed Warning and Warnings and Precautions* (5.1)]
- Seizures [see *Warnings and Precautions* (5.2)]
- Interaction with Alcohol [see *Warnings and Precautions* (5.3)]
- Accidental injury [see *Warnings and Precautions* (5.4)]
- Cardiovascular Events [see *Warnings and Precautions* (5.5)]
- Angioedema and hypersensitivity reactions [see *Warnings and Precautions* (5.6)]
- Serious skin reactions [see *Warnings and Precautions* (5.7)]

In the placebo-controlled studies, the most common adverse events associated with CHANTIX (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.

The treatment discontinuation rate due to adverse events in patients dosed with 1 mg twice daily was 12% for CHANTIX, compared to 10% for placebo in studies of three months' treatment. In this group, the discontinuation rates that are higher than placebo for the most common adverse events in CHANTIX-treated patients were as follows: nausea (3% vs. 0.5% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo).

Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness.

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During the premarketing development of CHANTIX, over 4500 subjects were exposed to CHANTIX, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less.

The most common adverse event associated with CHANTIX treatment is nausea, occurring in 30% of patients treated at the recommended dose,



compared with 10% in patients taking a comparable placebo regimen [see *Warnings and Precautions* (5.6)].

Table 5 shows the adverse events for CHANTIX and placebo in the 12-week fixed dose studies with titration in the first week [Studies 2 (titrated arm only), 4, and 5]. Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

MedDRA High Level Group Terms (HLGT) reported in  $\geq 5\%$  of patients in the CHANTIX 1 mg twice daily dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in  $\geq 1\%$  of CHANTIX patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as 'Insomnia', 'Initial insomnia', 'Middle insomnia', 'Early morning awakening' were grouped, but individual patients reporting two or more grouped events are only counted once.

**Table 5: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (HLGTs  $\geq 5\%$  of patients in the 1 mg BID CHANTIX Group and more commonly than placebo and PT  $\geq 1\%$  in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo)**

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	CHANTIX 0.5 mg BID N=129	CHANTIX 1 mg BID N=821	Placebo N=805
<b>GASTROINTESTINAL (GI)</b>			
GI Signs and Symptoms			
Nausea	16	30	10
Abdominal Pain *	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4
<b>PSYCHIATRIC DISORDERS</b>			
Sleep Disorder/Disturbances			
Insomnia **	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
<b>NERVOUS SYSTEM</b>			
Headaches			
Headache	19	15	13
Neurological Disorders			
NEC			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
<b>GENERAL DISORDERS</b>			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
<b>RESPIR/THORACIC/MEDI AST</b>			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0
Dyspnea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
<b>SKIN/SUBCUTANEOUS TISSUE</b>			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritis	0	1	1
<b>METABOLISM &amp; NUTRITION</b>			
Appetite/General Nutrit. Disorders			
Increased appetite	4	3	2
Decreased appetite/ Anorexia	1	2	1

\* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort

\*\* Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern and frequency of adverse events during the longer-term trials was similar to those described in Table 5, though several of the most common events were reported by a greater proportion of patients with long-term use (e.g., nausea was reported in 40% of patients treated with CHANTIX 1 mg twice daily in a one-year study, compared to 8% of placebo-treated patients).

Following is a list of treatment-emergent adverse events reported by patients treated with CHANTIX during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Blood and Lymphatic System Disorders. *Infrequent* anemia, lymphadenopathy. *Rare* leukocytosis, splenomegaly, thrombocytopenia.

Cardiac Disorders. *Infrequent* angina pectoris, arrhythmia, bradycardia, myocardial infarction, palpitations, tachycardia, ventricular extrasystoles. *Rare* acute coronary syndrome, atrial fibrillation, cardiac flutter, cor pulmonale, coronary artery disease.

Ear and Labyrinth Disorders. *Infrequent* tinnitus, vertigo. *Rare* deafness, Meniere's disease.

Endocrine Disorders. *Infrequent* thyroid gland disorders.

Eye Disorders. *Infrequent* conjunctivitis, dry eye, eye irritation, eye pain, vision blurred, visual disturbance. *Rare* acquired night blindness, blindness transient, cataract subcapsular, ocular vascular disorder, photophobia, vitreous floaters.

Gastrointestinal Disorders. *Frequent* diarrhea. *Infrequent* dysphagia, enterocolitis, eructation, esophagitis, gastritis, gastrointestinal hemorrhage, mouth ulceration. *Rare* gastric ulcer, intestinal obstruction, pancreatitis acute.

General Disorders and Administration Site Conditions. *Frequent* chest pain, edema, influenza-like illness. *Infrequent* chest discomfort, chills, pyrexia.

Hepatobiliary Disorders. *Infrequent* gall bladder disorder.

Investigations. *Frequent* liver function test abnormal, weight increased. *Infrequent* electrocardiogram abnormal, muscle enzyme increased, urine analysis abnormal.

Metabolism and Nutrition Disorders. *Infrequent* diabetes mellitus, hyperlipidemia, hypokalemia. *Rare* hypoglycemia.

Musculoskeletal and Connective Tissue Disorders. *Frequent:* arthralgia, back pain, muscle cramp, musculoskeletal pain, myalgia. *Infrequent* arthritis, osteoporosis. *Rare* myositis.

Nervous System Disorders. *Frequent* disturbance in attention, dizziness, sensory disturbance. *Infrequent* amnesia, migraine, parosmia, psychomotor hyperactivity, restless legs syndrome, syncope, tremor. *Rare* balance disorder, cerebrovascular accident, convulsion, dysarthria, facial palsy, mental impairment, multiple sclerosis, nystagmus, psychomotor skills impaired, transient ischemic attack, visual field defect.

Psychiatric Disorders. *Infrequent* disorientation, dissociation, libido decreased, mood swings, thinking abnormal. *Rare* bradyphrenia, euphoric mood.

Renal and Urinary Disorders. *Frequent* polyuria. *Infrequent* nephrolithiasis, nocturia, urethral syndrome, urine abnormality. *Rare* renal failure acute, urinary retention.

Reproductive System and Breast Disorders. *Rare* sexual dysfunction. *Frequent* menstrual disorder. *Infrequent* erectile dysfunction.

Respiratory, Thoracic and Mediastinal Disorders. *Frequent* epistaxis, respiratory disorders. *Infrequent* asthma. *Rare* pleurisy, pulmonary embolism.

Skin and Subcutaneous Tissue Disorders. *Frequent* hyperhidrosis. *Infrequent* acne, dry skin, eczema, erythema, psoriasis, urticaria. *Rare* photosensitivity reaction.

Vascular Disorders. *Frequent* hot flush. *Infrequent* thrombosis.

CHANTIX has also been studied in postmarketing trials including (1) a trial conducted in patients with chronic obstructive pulmonary disease (COPD), (2) a trial conducted in generally healthy patients (similar to those in the premarketing studies) in which they were allowed to select a quit date between days 8 and 35 of treatment ("alternative quit date instruction trial"), (3) a trial conducted in patients with stable cardiovascular disease and (4) a trial conducted in patients with stable schizophrenia or schizoaffective disorder.

Adverse events in the trial of patients with COPD and in the alternative quit date instruction trial were quantitatively and qualitatively similar to those observed in premarketing studies.

In the trial of patients with stable cardiovascular disease, more types and a greater number of cardiovascular events were reported compared to premarketing studies. Treatment-emergent (on-treatment or 30 days after treatment) cardiovascular events reported with a frequency  $\geq 1\%$  in either

treatment group in this study were angina pectoris (3.7% and 2.0% for varenicline and placebo, respectively), chest pain (2.5% vs. 2.3%), peripheral edema (2.0% vs. 1.1%), hypertension (1.4% vs. 2.6%), and palpitations (0.6 % vs. 1.1%). Deaths and serious cardiovascular events occurring over the 52 weeks of the study (treatment emergent and non-treatment emergent) were adjudicated by a blinded, independent committee. The following treatment-emergent adjudicated events occurred with a frequency  $\geq 1\%$  in either treatment group: nonfatal MI (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalization for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularization (2.0% vs. 0.6%), hospitalization for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina. Cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

In the trial of patients with stable schizophrenia or schizoaffective disorder, 128 smokers on antipsychotic medication were randomized 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up. The most common adverse events in patients taking varenicline were nausea (24% vs. 14.0% on placebo), headache (11% vs. 19% on placebo) and vomiting (11% vs. 9% on placebo). Among reported neuropsychiatric adverse events, insomnia was the only event that occurred in either treatment group in  $\geq 5\%$  of subjects at a rate higher in the varenicline group than in placebo (10% vs. 5%). These common and neuropsychiatric adverse events occurred on treatment or within 30 days after the last dose of study drug. There was no consistent worsening of schizophrenia in either treatment group as measured by the Positive and Negative Syndrome Scale. There were no overall changes in extra-pyramidal signs, as measured by the Simpson-Angus Rating Scale. The Columbia-Suicide Severity Rating Scale was administered at baseline and at clinic visits during the treatment and non-treatment follow-up phases. Over half of the patients had a lifetime history of suicidal behavior and/or ideation (62% on varenicline vs. 51% on placebo), but at baseline, no patients in the varenicline group reported suicidal behavior and/or ideation vs. one patient in the placebo group (2%). Suicidal behavior and/or ideation were reported in 11% of the varenicline-treated and 9% of the placebo-treated patients during the treatment phase. During the post-treatment phase, suicidal behavior and/or ideation were reported in 11% of patients in the varenicline group and 5% of patients in the placebo group. Many of the patients reporting suicidal behavior and ideation in the follow-up phase had not reported such experiences in the treatment phase. However, no new suicidal ideation or behavior emerged in either treatment group shortly (within one week) after treatment discontinuation (a phenomenon noted in post-marketing reporting). There were no completed suicides. There was one suicide attempt in a varenicline-treated patient. The limited data available from this single smoking cessation study are not sufficient to allow conclusions to be drawn.

## 6.2 Postmarketing Experience

The following adverse events have been reported during post-approval use of CHANTIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide in patients attempting to quit smoking while taking CHANTIX [see *Boxed Warning, Warnings and Precautions* (5.1)]. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking.

There have been post-marketing reports of new or worsening seizures in patients treated with CHANTIX [see *Warnings and Precautions* (5.2)].

There have been post-marketing reports of patients experiencing increased intoxicating effects of alcohol while taking CHANTIX. Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior [see *Warnings and Precautions* (5.1) and (5.3)].

There have been reports of hypersensitivity reactions, including angioedema [see *Warnings and Precautions* (5.6)].

There have also been reports of serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients taking CHANTIX [see *Warnings and Precautions* (5.7)].

There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischemic and hemorrhagic events in patients taking Chantix. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out.

## 7 DRUG INTERACTIONS

Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions [see *Clinical Pharmacology* (12.3)].

### 7.1 Use With Other Drugs for Smoking Cessation

Safety and efficacy of CHANTIX in combination with other smoking cessation therapies have not been studied.

**Bupropion:** Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers. The safety of the combination of bupropion and varenicline has not been established.

**Nicotine replacement therapy (NRT):** Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone. In this study, eight of twenty-two (36%) patients treated with the combination of varenicline and NRT prematurely discontinued treatment due to adverse events, compared to 1 of 17 (6%) of patients treated with NRT and placebo.

### 7.2 Effect of Smoking Cessation on Other Drugs

Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of CHANTIX use in pregnant women. In animal studies, CHANTIX caused decreased fetal weights, increased auditory startle response, and decreased fertility in offspring. CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive and developmental toxicity studies, pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. These exposures were 36 (rats) and 50 (rabbits) times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 1 mg twice daily. While no fetal structural abnormalities occurred in either species, reduced fetal weights occurred in rabbits at the highest dose (exposures 50 times the human exposure at the MRHD based on AUC). Fetal weight reduction did not occur at animal exposures 23 times the human exposure at the MRHD based on AUC.

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. These resulted in exposures up to 36 times the human exposure (based on AUC) at the MRHD of 1 mg twice daily. Decreased fertility and increased auditory startle response occurred in offspring.

### 8.3 Nursing Mothers

It is not known whether CHANTIX is excreted in human milk. In animal studies varenicline was excreted in milk of lactating animals. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

Safety and effectiveness of CHANTIX in pediatric patients have not been established.

### 8.5 Geriatric Use

A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see *Dosage and Administration* (2.2)].

No dosage adjustment is recommended for elderly patients.



## 8.6 Renal Impairment

Varenicline is substantially eliminated by renal glomerular filtration along with active tubular secretion. Dose reduction is not required in patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance <30 mL/min), and for patients with end-stage renal disease undergoing hemodialysis, dosage adjustment is needed. [see *Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

## 9 DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

Varenicline is not a controlled substance.

### 9.3 Dependence

**Humans** Fewer than 1 out of 1000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction.

In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers.

**Animals** Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine; however in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

## 10 OVERDOSAGE

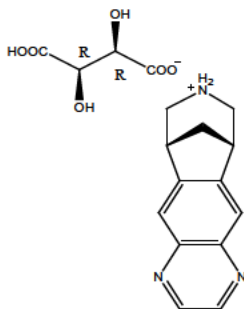
In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end stage renal disease [see *Clinical Pharmacology (12.3)*], however, there is no experience in dialysis following overdose.

## 11 DESCRIPTION

CHANTIX  $\square$ tablets contain varenicline (as the tartrate salt), which is a partial agonist selective for  $\alpha_4\beta_2$  nicotinic acetylcholine receptor subtypes.

Varenicline, as the tartrate salt, is a powder which is a white to off-white to slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-b][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water. Varenicline tartrate has a molecular weight of 361.35 Daltons, and a molecular formula of  $C_{13}H_{13}N_3 \cdot C_4H_6O_6$ . The chemical structure is:



CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "Pfizer" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablet debossed with "Pfizer" on one side and "CHX 1.0" on the other side. Each 0.5 mg CHANTIX tablet contains 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline free base; each 1mg CHANTIX tablet contains 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline free base. The following inactive ingredients are included in the tablets: microcrystalline cellulose, anhydrous dibasic calcium phosphate,

croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Varenicline binds with high affinity and selectivity at  $\alpha_4\beta_2$  neuronal nicotinic acetylcholine receptors. The efficacy of CHANTIX in smoking cessation is believed to be the result of varenicline's activity at  $\alpha_4\beta_2$  sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to these receptors.

Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to  $\alpha_4\beta_2$  neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate  $\alpha_4\beta_2$  receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to  $\alpha_4\beta_2$  receptors than to other common nicotinic receptors (>500-fold  $\alpha_3\beta_4$ , >3500-fold  $\alpha_7$ , >20,000-fold  $\alpha_1\beta\gamma\delta$ ), or to non-nicotinic receptors and transporters (>2000-fold). Varenicline also binds with moderate affinity ( $K_i = 350$  nM) to the 5-HT<sub>3</sub> receptor.

### 12.3 Pharmacokinetics

**Absorption/Distribution** Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was ~90%. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing. Plasma protein binding of varenicline is low ( $\leq 20\%$ ) and independent of both age and renal function.

**Metabolism/Elimination** The elimination half-life of varenicline is approximately 24 hours. Varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

**Pharmacokinetics in Special Patient Populations** There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

**Renal Impairment:** Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 mL/min and  $\leq 80$  mL/min). In subjects with moderate renal impairment (estimated creatinine clearance  $\geq 30$  mL/min and  $\leq 50$  mL/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >80 mL/min). In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD) undergoing a three-hour session of hemodialysis for three days a week, varenicline exposure was increased 2.7-fold following 0.5 mg once daily administration for 12 days. The plasma  $C_{max}$  and AUC of varenicline noted in this setting were similar to those of healthy subjects receiving 1 mg twice daily. [see *Dosage and Administration (2.2)*, and *Use in Specific Populations (8.6)*]. Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis [see *Overdosage (10)*].

**Geriatric Patients:** A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects.

**Pediatric Patients:** Because the safety and effectiveness of CHANTIX in pediatric patients have not been established, CHANTIX is not recommended for use in patients under 18 years of age. Single and multiple-dose pharmacokinetics of varenicline have been investigated in pediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight >55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg BID was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight  $\leq 55$  kg compared to that noted in the adult population.

**Hepatic Impairment:** Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment.

**Drug-Drug Interactions** Drug interaction studies were performed with varenicline and digoxin, warfarin, transdermal nicotine, bupropion, cimetidine, and metformin. No clinically meaningful pharmacokinetic drug-drug interactions have been identified.

*In vitro* studies demonstrated that varenicline does not inhibit the following cytochrome P450 enzymes (IC<sub>50</sub> >6400 ng/mL): 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline does not induce the cytochrome P450 enzymes 1A2 and 3A4.

*In vitro* studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (e.g., metformin [see below]) are unlikely to be affected by varenicline.

*In vitro* studies demonstrated the active renal secretion of varenicline is mediated by the human organic cation transporter OCT2. Co-administration with inhibitors of OCT2 (e.g., cimetidine [see below]) may not necessitate a dose adjustment of CHANTIX as the increase in systemic exposure to CHANTIX is not expected to be clinically meaningful. Furthermore, since metabolism of varenicline represents less than 10% of its clearance, drugs known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of CHANTIX [see *Clinical Pharmacology* (12.3)]; therefore, a dose adjustment of CHANTIX would not be required.

**Metformin:** When co-administered to 30 smokers, varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of metformin (500 mg twice daily), which is a substrate of OCT2. Metformin had no effect on varenicline steady-state pharmacokinetics.

**Cimetidine:** Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) to 12 smokers increased the systemic exposure of varenicline by 29% (90% CI: 21.5%, 36.9%) due to a reduction in varenicline renal clearance.

**Digoxin:** Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose in 18 smokers.

**Warfarin:** Varenicline (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R, S)-warfarin in 24 smokers. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics [see *Drug Interactions* (7.2)].

#### **Use with Other Drugs for Smoking Cessation**

**Bupropion:** Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers [see *Drug Interactions* (7.1)].

**Nicotine replacement therapy (NRT):** Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of adverse reactions was greater for the combination than for NRT alone [see *Drug Interactions* (7.1)].

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis** Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

**Mutagenesis** Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

**Impairment of Fertility** There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg twice daily). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg twice daily). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg twice daily).

## **14 CLINICAL STUDIES**

The efficacy of CHANTIX in smoking cessation was demonstrated in six clinical trials in which a total of 3659 chronic cigarette smokers (≥10 cigarettes per day) were treated with CHANTIX. In all clinical studies, abstinence from smoking was determined by patient self-report and verified by measurement of exhaled carbon monoxide (CO≤10 ppm) at weekly visits. Among the CHANTIX-treated patients enrolled in these studies, the completion rate was 65%. Except for the dose-ranging study (Study 1) and the maintenance of abstinence study (Study 6), patients were treated for 12 weeks and then were followed for 40 weeks post-treatment. Most patients enrolled in these trials were white (79-96%). All studies enrolled almost equal numbers of men and women. The average age of patients in these studies was 43 years. Patients on average had smoked about 21 cigarettes per day for an average of approximately 25 years. Patients set a date to stop smoking (target quit date) with dosing starting 1 week before this date.

Three additional studies were conducted in patients with cardiovascular disease, in patients with chronic obstructive pulmonary disease [see *Clinical Studies* (14.4)], and in patients instructed to select their quit date within days 8 and 35 of treatment [see *Clinical Studies* (14.5)].

In all studies, patients were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each weekly treatment visit according to Agency for Healthcare Research and Quality guidelines.

### **14.1 Initiation of Abstinence**

**Study 1** This was a six-week dose-ranging study comparing CHANTIX to placebo. This study provided initial evidence that CHANTIX at a total dose of 1 mg per day or 2 mg per day was effective as an aid to smoking cessation.

**Study 2** This study of 627 patients compared CHANTIX 1 mg per day and 2 mg per day with placebo. Patients were treated for 12 weeks (including one week titration) and then were followed for 40 weeks post-treatment. CHANTIX was given in two divided doses daily. Each dose of CHANTIX was given in two different regimens, with and without initial dose titration, to explore the effect of different dosing regimens on tolerability. For the titrated groups, dosage was titrated up over the course of one week, with full dosage achieved starting with the second week of dosing. The titrated and nontitrated groups were pooled for efficacy analysis.

Forty-five percent of patients receiving CHANTIX 1 mg per day (0.5 mg twice daily) and 51% of patients receiving 2 mg per day (1 mg twice daily) had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% of patients in the placebo group (Figure 1). In addition, 31% of the 1 mg per day group and 31% of the 2 mg per day group were continuously abstinent from one week after TQD through the end of treatment as compared to 8% of the placebo group.

**Study 3** This flexible-dosing study of 312 patients examined the effect of a patient-directed dosing strategy of CHANTIX or placebo. After an initial one-week titration to a dose of 0.5 mg twice daily, patients could adjust their dosage as often as they wished between 0.5 mg once daily to 1 mg twice daily per day. Sixty-nine percent of patients titrated to the maximum allowable dose at any time during the study. For 44% of patients, the modal dose selected was 1 mg twice daily; for slightly over half of the study participants, the modal dose selected was 1 mg/day or less.

Of the patients treated with CHANTIX, 40% had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% in the placebo group. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 9% of the placebo group.

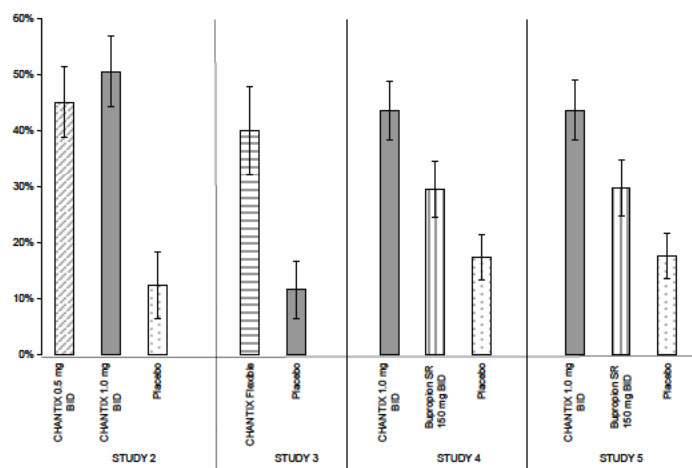
**Study 4 and Study 5** These identical double-blind studies compared CHANTIX 2 mg per day, bupropion sustained-release (SR) 150 mg twice daily, and placebo. Patients were treated for 12 weeks and then were followed for 40 weeks post-treatment. The CHANTIX dosage of 1 mg twice daily was achieved using a titration of 0.5 mg once daily for the initial 3 days followed by 0.5 mg twice daily for the next 4 days. The bupropion SR dosage of 150 mg twice daily was achieved using a 3-day titration of 150 mg once daily. Study 4 enrolled 1022 patients and Study 5 enrolled 1023 patients. Patients inappropriate for bupropion treatment or patients who had previously used bupropion were excluded.

In Study 4, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (17%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 12% of the placebo group and 23% of the bupropion SR group.

Similarly in Study 5, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (18%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group

were continuously abstinent from one week after TQD through the end of treatment as compared to 11% of the placebo group and 21% of the bupropion SR group.

**Figure 1: Continuous Abstinence, Weeks 9 through 12**



**Table 6: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)**

	CHANTIX 0.5 mg BID	CHANTIX 1 mg BID	CHANTIX Flexible	Bupropion SR	Placebo
Study 2	45% (39%, 51%)	51% (44%, 57%)			12% (6%, 18%)
Study 3		44% (38%, 49%)	40% (32%, 48%)		12% (7%, 17%)
Study 4		38% (32%, 44%)	32% (25%, 35%)	30% (25%, 35%)	17% (13%, 22%)
Study 5		44% (38%, 49%)	38% (32%, 44%)	30% (25%, 35%)	18% (14%, 22%)

BID = twice daily

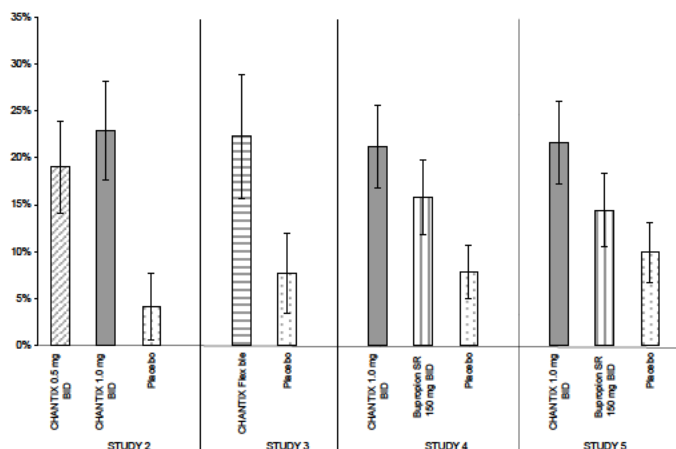
#### 14.2 Urge to Smoke

Based on responses to the Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal scale "urge to smoke" item, CHANTIX reduced urge to smoke compared to placebo.

#### 14.3 Long-Term Abstinence

Studies 1 through 5 included 40 weeks of post-treatment follow-up. In each study, CHANTIX-treated patients were more likely to maintain abstinence throughout the follow-up period than were patients treated with placebo (Figure 2, Table 7).

**Figure 2: Continuous Abstinence, Weeks 9 through 52**



**Table 7: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) across different studies**

	CHANTIX 0.5 mg BID	CHANTIX 1 mg BID	CHANTIX Flexible	Bupropion SR	Placebo
Study 2	19% (14%, 24%)	23% (18%, 28%)			4% (1%, 8%)
Study 3		21% (17%, 26%)	22% (16%, 29%)		8% (3%, 12%)
Study 4		17% (12%, 20%)	16% (11%, 18%)	16% (12%, 20%)	8% (5%, 11%)
Study 5		22% (17%, 26%)	14% (11%, 18%)	14% (11%, 18%)	10% (7%, 13%)

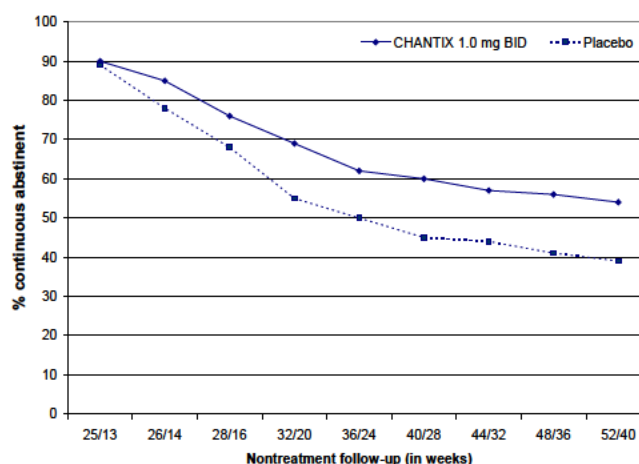
BID = twice daily

**Study 6** This study assessed the effect of an additional 12 weeks of CHANTIX therapy on the likelihood of long-term abstinence. Patients in this study (n=1927) were treated with open-label CHANTIX 1 mg twice daily for 12 weeks. Patients who had stopped smoking for at least a week by Week 12 (n= 1210) were then randomized to double-blind treatment with CHANTIX (1 mg twice daily) or placebo for an additional 12 weeks and then followed for 28 weeks post-treatment.

The continuous abstinence rate from Week 13 through Week 24 was higher for patients continuing treatment with CHANTIX (70%) than for patients switching to placebo (50%). Superiority to placebo was also maintained during 28 weeks post-treatment follow-up (CHANTIX 54% versus placebo 39%).

In Figure 3 below, the x-axis represents the study week for each observation, allowing a comparison of groups at similar times after discontinuation of CHANTIX; post-CHANTIX follow-up begins at Week 13 for the placebo group and Week 25 for the CHANTIX group. The y-axis represents the percentage of patients who had been abstinent for the last week of CHANTIX treatment and remained abstinent at the given timepoint.

**Figure 3: Continuous Abstinence Rate during Nontreatment Follow-Up**



#### 14.4 Subjects with Cardiovascular and Chronic Obstructive Pulmonary Disease

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged 35 to 75 years with stable, documented cardiovascular disease (diagnoses other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomized to CHANTIX 1 mg twice daily (n=353) or placebo (n=350) for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47%) compared to subjects treated with placebo (14%) and from week 9 through 52 (20%) compared to subjects treated with placebo (7%).

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged ≥ 35 years with mild-to-moderate COPD with post-bronchodilator FEV1/FVC <70% and FEV1 ≥ 50% of predicted normal value. Subjects were randomized to CHANTIX 1 mg twice daily (N=223) or placebo (N=237) for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (41%) compared to subjects treated with placebo (9%) and from week 9 through 52 (19%) compared to subjects treated with placebo (6%).



**Table 8: Continuous Abstinence (95% confidence interval), Studies in Patients with Cardiovascular Disease (CVD) and Chronic Obstructive Pulmonary Disease (COPD)**

	Weeks 9 through 12		Weeks 9 through 52	
	CHANTIX 1 mg BID	Placebo	CHANTIX 1 mg BID	Placebo
CVD Study	47% (42%, 53%)	14% (11%, 18%)	20% (16%, 24%)	7% (5%, 10%)
COPD Study	41% (34%, 47%)	9% (6%, 13%)	19% (14%, 24%)	6% (3%, 9%)

BID = twice daily

#### 14.5 Alternative Instructions for Setting a Quit Date

CHANTIX was evaluated in a double-blind, placebo-controlled trial where patients were instructed to select a target quit date between Day 8 and Day 35 of treatment. Subjects were randomized 3:1 to CHANTIX 1 mg twice daily (N=486) or placebo (N=165) for 12 weeks of treatment and followed for another 12 weeks post-treatment. Patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (54%) compared to patients treated with placebo (19%) and from weeks 9 through 24 (35%) compared to subjects treated with placebo (13%).

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "Pfizer" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablet debossed with "Pfizer" on one side and "CHX 1.0" on the other side. CHANTIX is supplied in the following package configurations:

	Description	NDC
Packs	Starting Month PAK (First month of therapy): Pack includes 1 card of 0.5 mg x 11 tablets and 3 cards of 1 mg x 14 tablets	NDC 0069-0471-97
	Continuing Month PAK (Continuing months of therapy): Pack includes 4 cards of 1 mg x 14 tablets	NDC 0069-0469-97
	Starting Month Box: 0.5 mg x 11 tablets and 1 mg x 42 tablets	NDC 0069-0471-02
	Continuing Month Box: 1 mg x 56 tablets	NDC 0069-0469-12
Bottles	0.5 mg - bottle of 56	NDC 0069-0468-56
	1 mg - bottle of 56	NDC 0069-0469-56

Store at 25 °C (77 °F); excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature).

#### 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

##### 17.1 Initiate Treatment and Continue to Attempt to Quit if Lapse

Instruct patients to set a date to quit smoking and to initiate CHANTIX treatment one week before the quit date. Alternatively, the patient can begin CHANTIX dosing and then set a date to quit smoking between days 8 and 35 of treatment. Encourage patients to continue to attempt to quit if they have early lapses after quit day [see Dosage and Administration (2.1)].

##### 17.2 How To Take

Advise patients that CHANTIX should be taken after eating, and with a full glass of water [see Dosage and Administration (2.1)].

##### 17.3 Starting Week Dosage

Instruct patients on how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. Explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening [see Dosage and Administration (2.1)].

##### 17.4 Continuing Weeks Dosage

Advise patients that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening [see Dosage and Administration (2.1)].

#### 17.5 Dosage Adjustment for CHANTIX or Other Drugs

Inform patients that nausea and insomnia are side effects of CHANTIX and are usually transient; however, advise patients that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.

Inform patients that some drugs may require dose adjustment after quitting smoking [see Dosage and Administration (2.1)].

#### 17.6 Counseling and Support

Provide patients with educational materials and necessary counseling to support an attempt at quitting smoking [see Dosage and Administration (2.1)].

#### 17.7 Neuropsychiatric Symptoms

Inform patients that some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation and suicide when attempting to quit smoking while taking CHANTIX. If patients develop agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to discontinue CHANTIX and report these symptoms to their healthcare provider immediately [see Boxed Warning, Warnings and Precautions (5.1), Adverse Reactions (6.2)].

#### 17.8 History of Psychiatric Illness

Encourage patients to reveal any history of psychiatric illness prior to initiating treatment.

#### 17.9 Nicotine Withdrawal

Inform patients that quitting smoking, with or without CHANTIX, may be associated with nicotine withdrawal symptoms (including depression or agitation) or exacerbation of pre-existing psychiatric illness.

#### 17.10 Seizures

Encourage patients to report any history of seizures or other factors that can lower seizure threshold. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately if they experience a seizure while on treatment [see Warnings and Precautions (5.2)].

#### 17.11 Interaction with Alcohol

Advise patients to reduce the amount of alcohol they consume while taking CHANTIX until they know whether CHANTIX affects their tolerance for alcohol [see Warnings and Precautions (5.3), Adverse Reactions (6.2)].

#### 17.12 Driving or Operating Machinery

Advise patients to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them [see Warnings and Precautions (5.4)].

#### 17.13 Cardiovascular Events

Patients should be instructed to notify their health care providers of symptoms of new or worsening cardiovascular events and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke. [see Warnings and Precautions (5.5), and Adverse Reactions (6.1)].

#### 17.14 Angioedema

Inform patients that there have been reports of angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue CHANTIX and immediately seek medical care if they experience these symptoms [see Warnings and Precautions (5.6), and Adverse Reactions (6.2)].

#### 17.15 Serious Skin Reactions

Inform patients that serious skin reactions, such as Stevens-Johnson Syndrome and erythema multiforme, were reported by some patients taking CHANTIX. Advise patients to stop taking CHANTIX at the first sign of rash with mucosal lesions or skin reaction and contact a healthcare provider immediately [see Warnings and Precautions (5.7), and Adverse Reactions (6.2)].

#### 17.16 Vivid, Unusual, or Strange Dreams

Inform patients that they may experience vivid, unusual or strange dreams during treatment with CHANTIX.

#### 17.17 Pregnancy and Lactation

Patients who are pregnant or breastfeeding or planning to become pregnant should be advised of: the risks of smoking to a pregnant mother and her developing baby, the potential risks of CHANTIX use during pregnancy and

breastfeeding, and the benefits of smoking cessation with and without CHANTIX [see *Use in Specific Populations* (8.1 and 8.3)].

This product's label may have been updated. For full prescribing information, please visit [www.pfizer.com](http://www.pfizer.com)



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## MEDICATION GUIDE

### CHANTIX® (CHANT-iks)

#### (varenicline) Tablets

#### What is the most important information I should know about CHANTIX?

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Some people have had serious side effects while using CHANTIX to help them quit smoking, including:

**New or worse mental health problems, such as changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions.** Some people had these symptoms when they began taking CHANTIX, and others developed them after several weeks of treatment, or after stopping CHANTIX.

**Before taking CHANTIX**, tell your doctor if you have ever had depression or other mental health problems. You should also tell your doctor about any symptoms you had during other times you tried to quit smoking, with or without CHANTIX.

**Stop taking CHANTIX and call your doctor right away** if you, your family, or caregiver notice agitation, hostility, depression or changes in your behavior or thinking that are not typical for you, or you develop any of the following symptoms:

- thoughts about suicide or dying, or attempts to commit suicide
- new or worse depression, anxiety, or panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused
- other unusual changes in behavior or mood

When you try to quit smoking, with or without CHANTIX, you may have symptoms that may be due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

**See "What are the possible side effects of CHANTIX?" for more information about other side effects.**

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#### What is CHANTIX?

CHANTIX is a prescription medicine to help people stop smoking.

Quitting smoking can lower your chances of having lung disease, heart disease or getting certain types of cancer that are related to smoking.

It is not known if CHANTIX is safe and effective in children.

It is not known if CHANTIX is safe and effective when used with other stop-smoking medicines.

### **Who should not take CHANTIX?**

Do not take CHANTIX if you have had a serious allergic or skin reaction to CHANTIX. Symptoms may include:

- swelling of the face, mouth (tongue, lips, gums), throat or neck
- trouble breathing
- rash, with peeling skin
- blisters in your mouth

### **What should I tell my doctor before taking CHANTIX?**

See **"What is the most important information I should know about CHANTIX?"**

Before you take CHANTIX, tell your doctor if you:

- use other treatments to quit smoking. Using CHANTIX with a nicotine patch may cause nausea, vomiting, headache, dizziness, upset stomach, and tiredness to happen more often than if you just use a nicotine patch alone.
- have kidney problems or get kidney dialysis. Your doctor may prescribe a lower dose of CHANTIX for you.
- have a history of seizures
- drink alcohol
- have heart or blood vessel problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if CHANTIX will harm your unborn baby.
- are breastfeeding. It is not known if CHANTIX passes into breast milk. You and your doctor should decide if you will breastfeed or take CHANTIX. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Your doctor may need to change the dose of some of your medicines when you stop smoking.

You should not use CHANTIX while using other medicines to quit smoking. Tell your doctor if you use other treatments to quit smoking.

Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist when you get a new medicine.

### **How should I take CHANTIX?**

- There are 2 ways that you can use CHANTIX to help you quit smoking. Talk to your doctor about the following 2 ways to use



CHANTIX:

Choose a **quit date** when you will stop smoking. Start taking CHANTIX 1 week (7 days) before your **quit date**.

**OR**

Start taking CHANTIX before you choose a **quit date**. Pick a date to quit smoking that is between days 8 and 35 of treatment.

Starting CHANTIX before your **quit date** gives CHANTIX time to build up in your body. You can keep smoking during this time. Take CHANTIX exactly as prescribed by your doctor.

- CHANTIX comes as a white tablet (0.5 mg) and a blue tablet (1 mg). You start with the white tablet and then usually go to the blue tablet. See the chart below for dosing instructions for adults.

<u>Day 1 to Day 3</u>	<ul style="list-style-type: none"><li>• <u>White</u> tablet (0.5 mg)</li><li>• Take 1 tablet each day</li></ul>
<u>Day 4 to Day 7</u>	<ul style="list-style-type: none"><li>• <u>White</u> tablet (0.5 mg)</li><li>• Take 1 in the morning and 1 in the evening</li></ul>
<u>Day 8 to end of treatment</u>	<ul style="list-style-type: none"><li>• <u>Blue</u> tablet (1 mg)</li><li>• Take 1 in the morning and 1 in the evening</li></ul>

- Make sure that you try to stop smoking on your **quit date**. If you slip-up and smoke, try again. Some people need to take CHANTIX for a few weeks for CHANTIX to work best.
- Most people will take CHANTIX for up to 12 weeks. If you have completely quit smoking by 12 weeks, your doctor may prescribe CHANTIX for another 12 weeks to help you stay cigarette-free.
- Take CHANTIX after eating and with a full glass (8 ounces) of water.
- This dosing schedule may not be right for everyone. Talk to your doctor if you are having side effects such as nausea, strange dreams, or sleep problems. Your doctor may want to reduce your dose.
- If you miss a dose of CHANTIX, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take your next dose at your regular time.

**What should I avoid while taking CHANTIX?**

- Use caution when driving or operating machinery until you know how CHANTIX affects you. CHANTIX may make you feel sleepy, dizzy, or have trouble concentrating, making it hard to drive or perform other activities safely.
- Decrease the amount of alcoholic beverages that you drink during treatment with CHANTIX until you know if CHANTIX affects your ability to tolerate alcohol. Some people have experienced the following when drinking alcohol during treatment with CHANTIX:
  - increased drunkenness (intoxication)
  - unusual or sometimes aggressive behavior
  - no memory of things that have happened

### What are the possible side effects of CHANTIX?

#### Serious side effects of CHANTIX may include:

- See **"What is the most important information I should know about CHANTIX?"**
- **Seizures.** Some people have had seizures during treatment with CHANTIX. In most cases, the seizures have happened during the first month of treatment with CHANTIX. If you have a seizure during treatment with CHANTIX, stop taking CHANTIX and contact your healthcare provider right away.
- **New or worse heart or blood vessel (cardiovascular) problems,** mostly in people, who already have cardiovascular problems. Tell your doctor if you have any changes in symptoms during treatment with CHANTIX.

#### Get emergency medical help right away if you have any of the following symptoms of a heart attack, including:

- chest discomfort (uncomfortable pressure, squeezing, fullness or pain) that lasts more than a few minutes, or that goes away and comes back
- pain or discomfort in one or both arms, back, neck, jaw or stomach
- shortness of breath, sweating, nausea, vomiting, or feeling lightheaded associated with chest discomfort
- **Allergic reactions** can happen with CHANTIX. Some of these allergic reactions can be life-threatening.
- **Serious skin reactions**, including rash, swelling, redness, and peeling of the skin. Some of these skin reactions can become life-threatening.

#### Stop taking CHANTIX and get medical help right away if you have any of the following symptoms:

- swelling of the face, mouth (tongue, lips, and gums), throat or neck
- trouble breathing
- rash with peeling skin
- blisters in your mouth

#### The most common side effects of CHANTIX include:

- nausea
- sleep problems (trouble sleeping or vivid, unusual, or strange dreams)
- constipation
- gas
- vomiting

Tell your doctor about side effects that bother you or that do not go away.

These are not all the side effects of CHANTIX. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### How should I store CHANTIX?

- Store CHANTIX at room temperature, between 68°F to 77°F (20°C to 25°C).
- **Keep CHANTIX and all medicines out of the reach of children.**

### General information about CHANTIX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CHANTIX for a condition for which it was not prescribed. Do not give your CHANTIX to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CHANTIX that is written for healthcare professionals.

For more information about CHANTIX and tips on how to quit smoking, go to [www.CHANTIX.com](http://www.CHANTIX.com) or call 1-877-242-6849.

#### **What are the ingredients in CHANTIX?**

**Active ingredient:** varenicline tartrate

**Inactive ingredients:** microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

This Medication Guide has been approved by the U.S. Food and Drug Administration.



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