



**Pediatric Focused Safety Review:
Chantix[®] (varenicline tartrate)
Pediatric Advisory Committee Meeting
September 19, 2013**

Erica D. Radden, MD

**Pediatric and Maternal Health Staff
Office of New Drugs**

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

Outline

- Background Information
- Pediatric Studies
- Pediatric Labeling Changes
- Additional Relevant Safety Labeling
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information Chantix[®] (varenicline tartrate)

- **Drug:** Chantix[®] (varenicline tartrate)
- **Therapeutic Category:** partial agonist selective for $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes
- **Indication:** For use as an aid to smoking cessation treatment.
- **Formulation:** 0.5 mg and 1 mg tablets.
- **Sponsor:** Pfizer, Inc.

Background Drug Information Chantix[®] (varenicline tartrate)

- **Dosage and Administration:**
 - Start taking Chantix and then quit smoking between days 7 and 35 of treatment.
 - Week 1: 0.5 mg once daily on days 1-3; 0.5 mg twice daily on days 4-7.
 - Week 2-12: 1 mg twice daily.
 - An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence.

Background Drug Information

Chantix[®] (varenicline tartrate)

- **Original Market approval:** May 10, 2006
 - PREA studies waived in patients <12 years of age
 - PREA studies deferred in patients 12-16 years of age
 - Multiple dose pharmacokinetic (PK) study-completed
 - Safety and efficacy study- ongoing
 - Single dose PK study in 12-16 year olds included in labeling

Background Drug Information

Chantix[®] (varenicline tartrate)

- **Pediatric labeling changes: November 9, 2011**
 - Fulfilled first PREA requirement.
 - Safety and effectiveness of Chantix in pediatric patients have not been established.
 - Chantix is not recommended for use in patients <18 years of age.
 - Information added from postmarketing multiple-dose PK study of varenicline in pediatric patients 12-17 years of age (Pharmacokinetics section, 12.3).

Background Drug Information Chantix[®] (varenicline tartrate)

- **Additional Outstanding Postmarketing Requirements:**
 - Prospective epidemiologic cohort study of varenicline exposure in pregnant smokers.
 - Clinical trial and follow-up extension study to compare the risk of clinically significant neuropsychiatric events in individuals using varenicline, bupropion, nicotine replacement therapy, or placebo.

Pediatric Studies

Chantix[®] (varenicline tartrate)

- Two randomized, double-blind, placebo-controlled studies to evaluate the pharmacokinetics (PK), safety and tolerability of varenicline in healthy adolescent (12-17 years of age) smokers:
 - **Single-Dose** PK study (results included in labeling upon approval in May 2006)
 - **Multiple-Dose** PK study (results included in labeling change in November 2011)

Pediatric Labeling Changes

Chantix[®] (varenicline tartrate)

12.3 Pharmacokinetics, Pediatric Patients

- PK was 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 was comparable to that noted for the same doses in the adult population.
- At a dose of 0.5 mg twice a day, the steady-state daily exposure of varenicline was approximately 40% higher in adolescent patients with bodyweight ≤55 kg compared to the adult population.

Relevant Safety Labeling

Chantix[®] (varenicline tartrate)

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)

Relevant Safety Labeling

Chantix[®] (varenicline tartrate)

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
- 5.2 Angioedema and Hypersensitivity Reactions
- 5.3 Serious Skin Reactions
- 5.4 Cardiovascular (CV) Events (In a meta-analysis of 15 clinical trials, all-cause and cardiovascular mortality was lower in patients treated with Chantix.)
- 5.5 Accidental Injury (e.g. traffic accidents)
- 5.6 Nausea (most common adverse reaction)

Relevant Safety Labeling

Chantix[®] (varenicline tartrate)

6 ADVERSE REACTIONS

Common Adverse Events (AEs) in placebo-controlled studies (>5% and twice the rate of placebo-treated patients):

- Nausea, abnormal (vivid, unusual or strange) dreams, constipation, flatulence and vomiting

AEs in Chantix-treated* patients associated with discontinuation rates that are higher than placebo:

- Nausea, insomnia and abnormal dreams

* Dose: 1 mg BID

Relevant Safety Labeling

Chantix[®] (varenicline tartrate)

6 ADVERSE REACTIONS:

6.1 Clinical Trials Experience, Postmarketing Trials

- Chronic Obstructive Pulmonary Disease patients and healthy patients with alternative quit date- AEs similar to premarketing studies
- Stable CV disease
 - treatment-emergent AEs: nonfatal MI, angina
 - CV mortality lower in Chantix arm
- Stable schizophrenia or schizoaffective disorder patients
 - Most common AEs: nausea, headache and vomiting
 - No consistent worsening of schizophrenia or overall changes in extrapyramidal signs
 - Suicidal behavior/ideation slightly increased in Chantix arm

Relevant Safety Labeling

Chantix[®] (varenicline tartrate)

6 ADVERSE REACTIONS

6.2 Postmarketing Experience

- 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)*]
- Myocardial infarction and cerebrovascular accident including ischemic and hemorrhagic events



Chantix[®] Drug Utilization Prescriptions¹ and Patients² U.S. Outpatient Retail Pharmacy Setting May 2006 – February 2013, cumulative

	Prescriptions ¹		Patients ²	
	N	Share %	N	Share %
Chantix TOTAL	25,471,528	100.0	10,109,233*	100.0
0-17 years	34,719	0.1	22,999*	0.2
0-5 years	3,466	10.0	2,382	10.4
6-11 years	4,166	12.0	2,796	12.2
12-17 years	27,087	78.0	17,901	77.8
18+ years	25,436,809	99.9	10,088,190	99.8
Unspecified Age	898	< 0.1%	567	< 0.1%

* 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.

¹IMS, Vector One[®]: National (VONA). May 2006 – February 2013. Extracted May 2013.

²Total Patient Tracker (TPT). May 2006 – February 2013. Extracted May 2013.



Chantix[®] Drug Utilization Prescriptions¹ and Patients² U.S. Outpatient Retail Pharmacy Setting May 2006 – February 2013, cumulative

	Prescriptions ¹		Patients ²	
	N	Share %	N	Share %
Chantix TOTAL	25,471,528	100.0	10,109,233*	100.0
0-17 years	34,719	0.1	22,999*	0.2
0-5 years	3,466	10.0	2,382	10.4
6-11 years	4,166	12.0	2,796	12.2
12-17 years	27,087	78.0	17,901	77.8
18+ years	25,436,809	99.9	10,088,190	99.8
Unspecified Age	898	< 0.1%	567	< 0.1%

* 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.

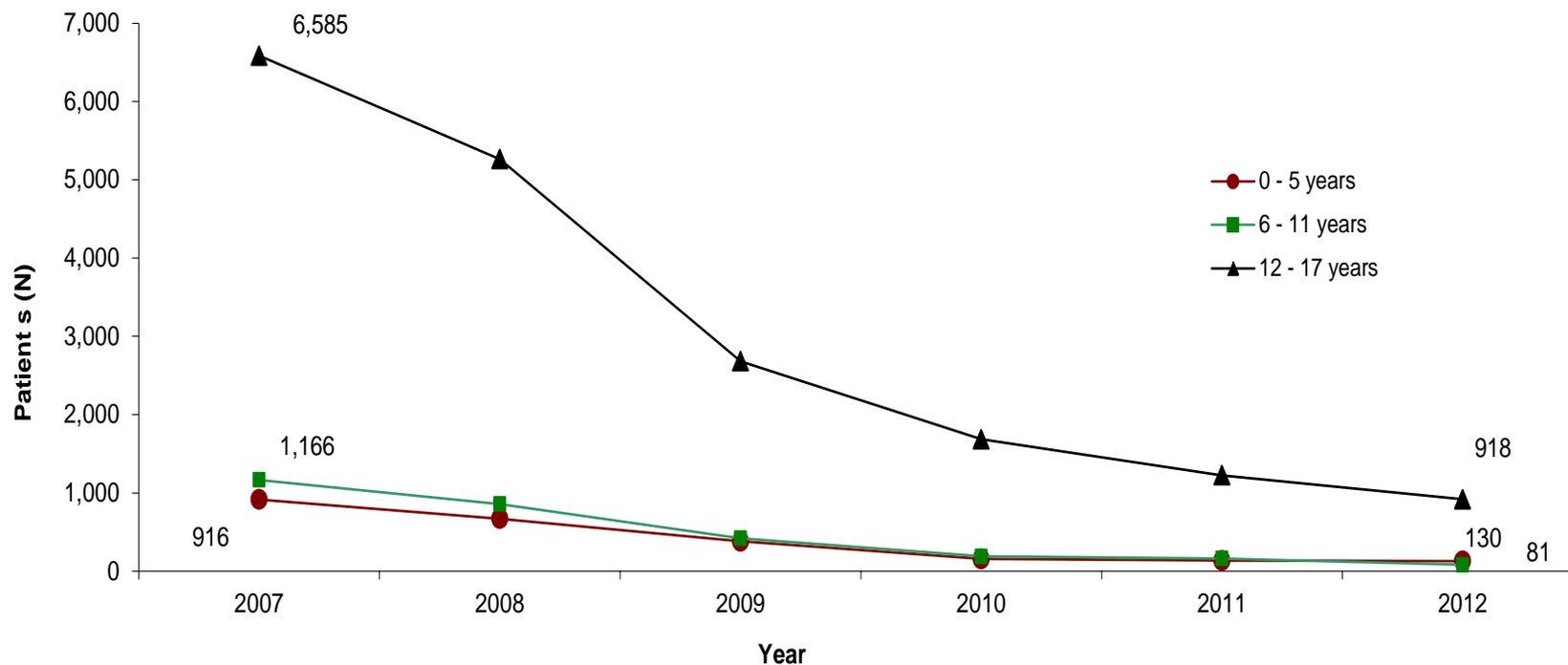
¹IMS, Vector One[®]: National (VONA). May 2006 – February 2013. Extracted May 2013.

²Total Patient Tracker (TPT). May 2006 – February 2013. Extracted May 2013.

Chantix® Drug Utilization

Trend graph for pediatric patients

Nationally estimated number of pediatric patients who received a prescription for Chantix® products dispensed through U.S. retail pharmacies, stratified by ages 0-5, 6-11, 12-17 years, from year 2007 through 2012, annually



Source: IMS Health, Vector One®: Total Patient Tracker. Extracted May 2013

Total Number of Chantix[®] Adverse Event Reports* Since Approval date (May 10, 2006 to February 19, 2013)

	All reports (US) [^]	Serious [†] (US)	Death (US)
Adults (≥ 18 yrs.)	36,182 (30,719)	19,612 (14,226)	740 (560)
Pediatrics (0-17 yrs.)	46 (40)	23 (17)	0 (0)
Unknown Age (Null values)	21,788 (20,027)	7,735 (6,009)	333 (285)**
Total	58,016 (50,786)	27,370 (20,252)	1,073 (845)

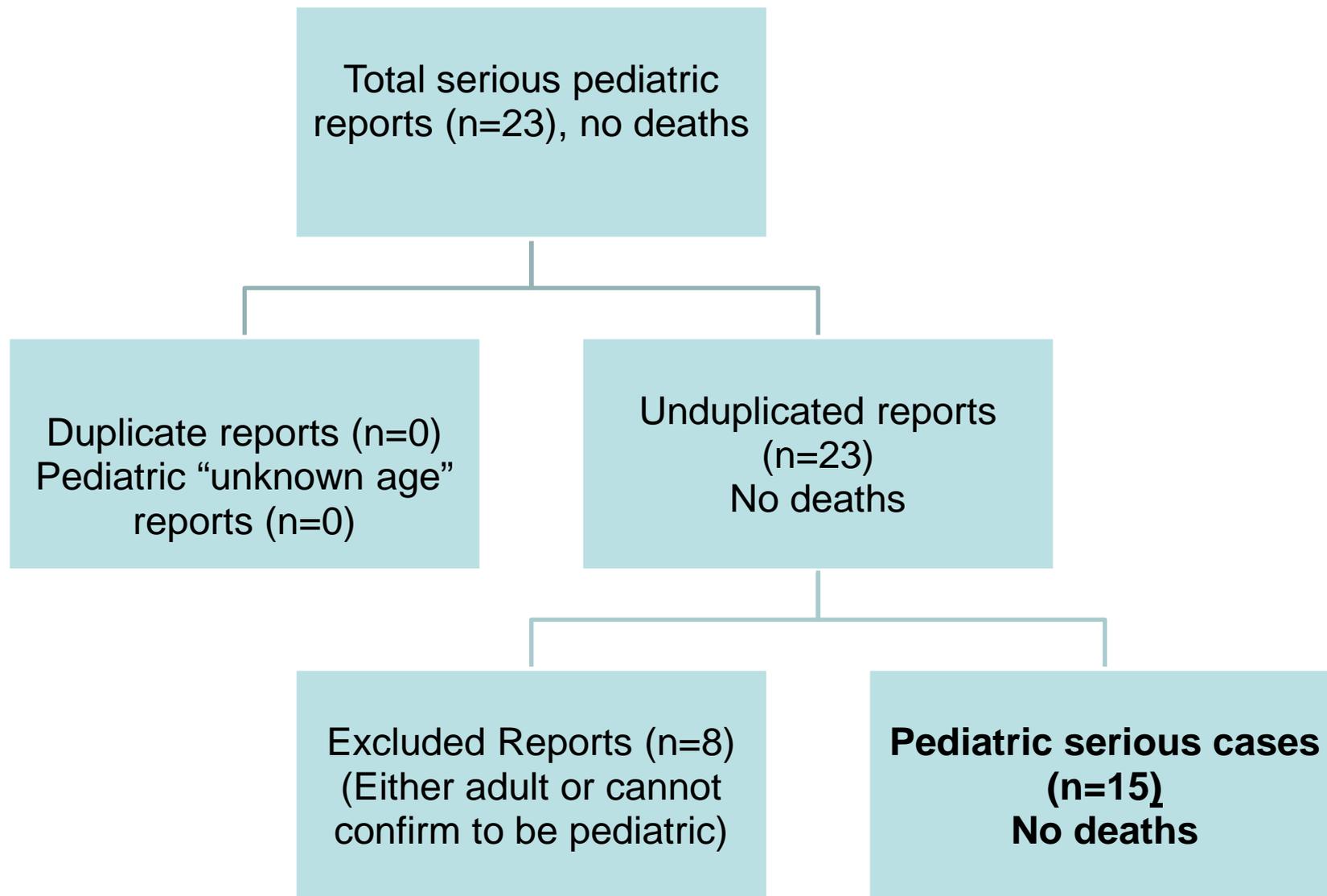
*May include duplicates and have not been assessed for causality

[^] US counts in parentheses

[†] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

** No pediatric deaths identified.

Selection of Serious Pediatric AERS Cases



Serious Non-Fatal Adverse Events (n=15) Chantix[®] (varenicline tartrate)

Characteristics

- Age (n=15)
 - 22 months (n=1)
 - 14-17 years (n=14)

Reason for Chantix Use:

- Smoking Cessation (n=11)
 - Psychiatric (n=8)
 - Non-psychiatric (n=3)
- Non-prescribed (n=3)
- Accidental Exposure (n=1)

Serious Non-Fatal Adverse Events (n=15)

Chantix[®] (varenicline tartrate)

- **Psychiatric (n=11)**
 - Prescribed use (n=8)
 - Non-prescribed use (n=3)
- **Non-psychiatric (n=3)**
- **Accidental Exposure (n=1)**

Serious Non-Fatal Adverse Events Chantix[®] (varenicline tartrate) Psychiatric Events (n=11)

Labeled Psychiatric Patient Terms from Reports

Suicide attempt	Suicidal Ideation
Depression/Crying	Emotional Disorder
Anger	Feeling abnormal
Intentional overdose/self-injury	Mental Disorder
Irritability	Mood altered/Mood swings
Abnormal behavior	Thinking abnormal
Aggression	Anxiety/Anxiety Disorder

Note: Multiple terms have been reported for some single patients

Labeling- multiple neuropsychiatric symptoms, worsening of pre-existing psychiatric illness and suicidality (Boxed Warning, Warning and Precautions, Adverse Reactions, Patient Counseling Information)

Serious Non-Fatal Adverse Events Chantix[®] (varenicline tartrate) Psychiatric Events (n=11)

Unlabeled Psychiatric Patient Terms from Reports

- Adjustment Disorder with Mixed Disturbance of Emotion and Conduct
- Bipolar Disorder
- Post-Traumatic Stress Disorder

Underlined (unlabeled) disorders were pre-existing conditions associated with cases with prescribed Chantix use

*Unlabeled events are underlined

Serious Non-Fatal Adverse Events Chantix[®] (varenicline tartrate) Psychiatric Events (n=11)

Prescribed use (n=8)

- 3 suicide attempts
 - Cutting wrists (n=2)
 - Prescription Drug Overdose with Depakote (n=1)
- 6 cases with prior psychiatric illness and/or concomitant use of psychiatric medications
- 2 cases with minimal or no medical history

Insufficient clinical information in these 8 cases to establish a direct association with varenicline use.

Serious Non-Fatal Adverse Events Chantix[®] (varenicline tartrate) Psychiatric Events (n=11)

Non-prescribed use (n=3)

- 14 and 16 year old attempted suicide by taking multiple varenicline tablets (6 mg and 15 mg total dose, respectively).
 - 14 year old developed nausea and hypotension; outcome unknown.
 - 16 year old developed tachycardia, hypertension, tachypnea and vomiting; recovered.

Related labeling- hypertension in CV disease trial (Adverse Reactions)

- 16 year old smoker attempted suicide by overdosing on unspecified prescription medications while taking mother's Chantix.

Role of varenicline could not be established due to insufficient clinical information.

Labeling- Overdosage: standard supportive measures recommended

*Unlabeled events are underlined.

Serious Non-Fatal Adverse Events

Chantix[®] (varenicline tartrate)

Non-Psychiatric Events (n=3)

- Increased blood glucose
 - Patient with history of Diabetes
 - Labeling- Diabetes (Adverse Reactions)*
- Hematuria/vaginal hemorrhage
 - Symptoms started after 5 doses of varenicline, no concomitant medications or relevant history, bloodwork normal, symptoms resolved after discontinuation.
 - Related labeling- urine abnormality and menstrual disorder (Adverse Reactions)*
- Increased blood carbon monoxide (CO)
 - Reporting physician attributed elevated CO to the patient smoking

*Unlabeled events are underlined.

Serious Non-Fatal Adverse Events

Chantix[®] (varenicline tartrate)

Accidental Exposure (n=1)

- 22 month female with unknown medical history and concomitant medications accidentally ingested 1 mg varenicline tablet. She recovered after experiencing vomiting and a “fuzzy head” in a “twilight state” reported by her parent.

Labeling- Vomiting, disorientation, abnormal thinking (Adverse Reactions)

Pediatric Focused Safety Review Summary

Chantix[®] (varenicline tartrate)

- This concludes the pediatric focused safety review.
- Labeling has been updated to include the results of the pharmacokinetic study in adolescents performed under PREA.
- The safety review identified no new safety signals.
- FDA recommends continuing routine monitoring.
- Does the Committee concur?



ACKNOWLEDGEMENTS

Division of Anesthesia, Analgesia and Addiction Products

Rigoberto Roca, MD
Jessica Eisner, MD
Celia Winchell, MD
Ayanna Augustus, PhD

PMHS

Denise Pica-Branco, PhD
Hari Cheryl Sachs, MD
Lynne Yao, MD

OPT

Judith Cope, MD, MPH
Dianne Murphy, MD
Amy Odegaard, MPH
Pam Weinel, RN, MS, MBA

OSE

Justin Mathew, PharmD
Hina Mehta, PharmD
Laura Governale, PharmD, MBA
Martin Pollock, PharmD
Jane Gilbert, MD, PhD
Peter Diak, PharmD, MPH
Shewit Bezabeh, MD
Min Chen, MS, RPh



Back-up Slides