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Office of Surveillance and Epidemiology**

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antiviral products  
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Symmetrel®(amantadine); Flumadine® (rimantadine)  
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Flumadine® (rimantadine)  
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## EXECUTIVE SUMMARY

At the November 2005 Pediatric Advisory Committee, the committee requested that FDA conduct a comprehensive review of neuropsychiatric events with antivirals for influenza after two additional influenza seasons. Since that time, the **PRECAUTIONS** section of the U.S. label for oseltamivir was updated in November 2006 to include post-marketing reports of self-injury and delirium and advise that patients be monitored during treatment. In March 2007, the Japanese Ministry of Health, Labor, and Welfare restricted the use of oseltamivir in patients aged 10-19 years.

Additional safety information will soon be available for oseltamivir, according to a recent update provided by the Japanese Ministry of Health, Labor and Welfare (MHLW). Chugai Pharmaceutical Co, Ltd. will be conducting a sleep laboratory study of oseltamivir. In addition, safety information will also be obtained from an epidemiological survey study of 10,000 cases (approximately 700 medical institutions). The survey will attempt to more precisely examine the time relationship between observed symptoms and drug use, targeting patients less than 18 years of age. There is also a national survey in Japan to gather case reports from medical institutions of influenza-associated abnormal behaviors from last flu season and this upcoming flu season. We await the results from these studies to help clarify the possible contribution of oseltamivir to the development of neuropsychiatric events in patients with influenza.

This comprehensive review examined post-marketing reports of neuropsychiatric events for oseltamivir, zanamivir, amantadine, and rimantadine. FDA's postmarketing Adverse Event Reporting System (AERS) database was searched using a broad search strategy of 51 High Level Terms (HLTs) for neuropsychiatric events (see Appendix 1. Search Criteria). Before presenting AERS data, it is important to consider that there are complexities in adequately assessing a clear relationship of neuropsychiatric events to drug use. First, the majority of the reports reviewed were foreign reports that were translated, which makes it difficult to capture an accurate description of an adverse event. Second, the MedDRA coding of the adverse event is not consistent among the foreign reports because they are subject to the choice of words from different translators. Third, many events such as convulsions, delirium, and depressed level of consciousness are complications of viral encephalitis secondary to influenza making it difficult to distinguish between complications of the virus, potential adverse effects of drugs, or a combination of both.

In order to provide some level of consistency in the assessment of these cases, the narrative for each of the cases was manually reviewed and the cases were grouped into the following **nine** categories according to the primary neuropsychiatric event described in the narratives from each case. These categories were developed specifically for this case series.

- **ANX** – Anxiety/fear without hallucinations
- **DIB** – Delirium with impulsive behavior & injury
- **DEL** – Delirium, delusion, hallucination, psychosis
- **DLC** – Depressed level of consciousness
- **LOC** – Loss of consciousness, syncope
- **MSC** – Miscellaneous
- **PAN** – Panic attacks
- **SUI** – Suicidal events
- **SZ** – Seizures, convulsion

In addition, the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV)<sup>1</sup> was useful in establishing the nine categories of neuropsychiatric events as described above and in substantiating that these abnormal behaviors may be substance-induced delirium due to a medication for this review. The text on diagnostic features (page 124) states that “the essential feature of a delirium is a disturbance of consciousness that is accompanied by a change in cognition that cannot be better accounted for by a preexisting or evolving dementia. The disturbance develops over a short period of time, usually hours to days, and tends to fluctuate during the course of the day. There is evidence from the history, physical examination, or laboratory tests that the delirium is a direct physiological consequence of a general medical condition, substance intoxication to withdrawal, use of a medication, or toxin exposure, or a combination of these factors.”

According to DSM-IV, clinical hallmarks of delirium which are relevant to the evaluation of these case reports include impaired attention, distractibility, cognitive impairment, disorientation, and perceptual disturbances including hallucinations. Patients may react emotionally and behaviorally to hallucinations. The time course of delirium is notable for rapid onset with fluctuations throughout the course of the day. It is thought that children may be more susceptible to delirium from fever or medications than adults.

The pertinent findings and recommendations from this comprehensive review of post-marketing adverse event reports for the four marketed products for influenza treatment and prophylaxis are briefly summarized below.

## NEURAMINIDASE INHIBITORS

### 1. Tamiflu (oseltamivir)

#### 1.1 Background

Oseltamivir is approved in the U.S. for the treatment and prophylaxis of influenza in patients  $\geq 1$  year. It is available as an oral capsule and suspension. Neuropsychiatric events are described in the **PRECAUTIONS** section of the U.S. labeling as follows: *There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout treatment.* Syncope and seizures are listed under **ADVERSE REACTIONS**.

#### 1.2 AERS search results

A total of 728 AERS reports were retrieved using the broad search strategy. These reports were reviewed and duplicates and irrelevant reports were excluded, resulting in **596 cases**. The majority of these 596 cases occurred in patients  $\leq 21$  years of age (61%) and were from Japan (75%). These events had a short latency (median onset = 24 hours, after a median of 1 or 2 doses) and resolved quickly (median = 6 hours). Nineteen cases reported oseltamivir use for influenza prophylaxis. However, only one prophylaxis case reported psychosis and hallucinations, but the case was confounded by possible marijuana use in a teenage patient. There were no reports of Delirium with impulsive behavior and injury following the use of oseltamivir for influenza prophylaxis.

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<sup>1</sup> Delirium, Dementia, and Amnesic and Other Cognitive Disorders section. *Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition.* American Psychiatric Association Washington DC. Pages:123-133.

The reports categorized as Delirium with impulsive behavior and self-injury (n=59) and Delirium, delusions, hallucinations or psychosis (n= 225) accounted for 48% of all neuropsychiatric cases for oseltamivir. There were 5 reports of delirium in pediatric patients that resulted in a fatal outcome; all occurred in Japan. There were 3 reports of completed suicide in adult patients. To date there are no fatalities in the U.S. caused by neuropsychiatric events that are causally related to oseltamivir use.

### 1.3 Conclusions

This comprehensive review of 596 cases of neuropsychiatric events did not further clarify whether these events are related to oseltamivir, disease or a combination of drug-disease expression, particularly in pediatric patients. However, the postmarketing data for oseltamivir continue to suggest a possible association between the use of oseltamivir and the development of neuropsychiatric events.

The current labeling for oseltamivir provides limited descriptive information about neuropsychiatric events. We recommend an update to the **PRECAUTIONS** section on **Neuropsychiatric Events** to note that some cases in Japanese adult and pediatric patients resulted in a fatal outcome. Since these events continue to be reported despite labeling, the **PRECAUTION** section should also provide additional details about these events, including the abrupt onset (after 1 or 2 doses) and subsequent serious injury sometimes despite monitoring by a family member. Consideration should be given to providing further risk communication (e.g. Public Health Advisory, Prescriber Alert) to further describe the characteristics of these cases and the need for monitoring. A restriction on the use of oseltamivir in the U.S. does not seem warranted at this time based on the post-marketing data and the still unanswered question about whether these events are due to oseltamivir, influenza/fever, or a combination of the two.

## 2. Relenza (zanamivir)

### 2.1 Background

Zanamivir is an oral inhalation powder approved in the U.S. for the treatment of influenza in patients  $\geq 7$  years and prophylaxis of influenza in patients  $\geq 5$  years. The U.S. labeling states that syncope and seizures have been observed during clinical practice. As an oral inhalation powder, zanamivir has a unique pharmacokinetic profile, with systemic absorption of only approximately 4% to 17% of the inhaled dose.

### 2.2 AERS search results

A total of 166 reports in the AERS database for zanamivir were retrieved using the broad search strategy. The reports were reviewed and duplicates and reports not describing a neuropsychiatric event of interest were excluded, resulting in a total of **115 cases**. Of the 115 zanamivir cases, 74 (64%) occurred in patients  $\leq 21$  years of age and 81 (70%) were from Japan. There were no cases where zanamivir was used for influenza prophylaxis. We categorized 7 reports as Delirium with impulsive behavior and self-injury in which the patient expressed “fear” and attempted to flee or expressed a desire to “jump.” None of these events were fatal.

### 2.3 Conclusions

A search of the AERS database retrieved 115 cases of neuropsychiatric events with zanamivir. Many of these reports share the same characteristics as the reports we have previously reviewed with oseltamivir. The zanamivir cases provide conflicting evidence as to whether these events are drug-related only, disease manifestation alone, or a combination of drug-disease expression. There are several factors that suggest that these events are due to influenza alone, including the low

systemic absorption of zanamivir with its low potential to penetrate into the CNS, short latency, event occurrence during fever, and lack of reoccurrence with subsequent dosing. However, a potential causal role for zanamivir is suggested by the reoccurrence of neuropsychiatric events after each dose with multiple dosing. On balance, we feel the propensity of the evidence favors an influenza-induced etiology, however, we cannot entirely rule out a possible contribution of zanamivir in the development of these neuropsychiatric events over and above the adverse symptoms which may result from the natural history of influenza-illness.

Despite the uncertainty about the causal role of zanamivir, it seems prudent at this time to caution prescribers and patients about these adverse events observed in patients treated with zanamivir. We recommend adding a statement to the zanamivir label under **PRECAUTIONS** noting that postmarketing reports of hallucinations, delirium, and abnormal behavior have been observed in patients receiving zanamivir for the treatment of influenza. We also recommend including a statement that patients with influenza should be closely monitored for signs of abnormal behavior throughout treatment.

#### **2.4. Recommendations regarding Neuraminidase Inhibitors**

The postmarketing reports of neuropsychiatric adverse events with zanamivir, particularly delirium and abnormal behavior, raise the question as whether these events may be due to the neuraminidase inhibitor class. Although there is still uncertainty about the cause of the reported abnormal behavior in patients receiving neuraminidase inhibitors for treatment of influenza, it seems prudent for the labeling for both products to contain language about postmarketing reports of hallucinations, delirium, and abnormal behavior in the **PRECAUTIONS** section. Both labels should have a statement that patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period, especially during the first few days after initiating treatment.

It is significant that fatalities have occurred with oseltamivir, including cases where the patient was being monitored by a parent or guardian. The following should be added to the **PRECAUTIONS** section on *Neuropsychiatric Events* in the oseltamivir labeling: fatalities have occurred in adult and pediatric patients in Japan, the onset may be abrupt, and fatal events have occurred even while the patient was being monitored. No restrictions for the neuraminidase inhibitors seem warranted at this time in U.S. patients based on the current post-marketing data. Consideration should be given to providing further risk communication (e.g. Public Health Advisory, Prescriber Alert) to further describe these cases and emphasize the importance of close monitoring, particularly in pediatric patients. We will continue to monitor the post-marketing data for these products.

## **M2 INHIBITORS**

### **3. Symmetrel (amantadine)**

#### **3.1 Background**

Amantadine is approved in the U.S. for the treatment and prophylaxis of influenza A in patients aged  $\geq 1$  year. The current U.S. labeling for amantadine has extensive information about neuropsychiatric events, including a **WARNING** about suicide attempts and an increase in seizures in patients with a history of epilepsy. The **WARNING** also states that amantadine can exacerbate mental problems in patients with a history of psychiatric disorders and patients may exhibit disorientation, confusion, depression, personality changes, agitation, aggressive behavior, hallucinations, paranoia, other psychotic reactions, somnolence or insomnia. Other neuropsychiatric events reported include: coma, stupor, delirium, delusions, aggressive behavior, paranoid reaction, manic reaction, EEG changes, and tremor. Abrupt discontinuation of amantadine

may also precipitate delirium, agitation, delusions, hallucinations, paranoid reaction, stupor, anxiety, depression and slurred speech.

### **3.2 AERS search results**

A total of 840 reports of neuropsychiatric events were retrieved from the AERS database for amantadine. The review focused on **42 unduplicated cases** of neuropsychiatric events in pediatric patients (age  $\leq$  21 years). Amantadine was prescribed for influenza treatment in 28 patients, influenza prophylaxis in 6 patients and other indications in 8 patients.

There were no reports of Delirium with impulsive behavior and injury in pediatric patients. There were 3 cases of Suicidal events in pediatric patients (range 17-19 years). The majority of neuropsychiatric events were classified as Delirium, delusions, hallucinations, psychosis (n = 18) or Depressed level of consciousness (n = 7). Two patients who experienced confusion and hallucinations had temperatures of 102 and 104 degrees F. Seizures were reported in 7 patients (range 3-12 years). Neuropsychiatric events were observed in two patients treated with amantadine and oseltamivir. "Fear" and "nightmares" were reported in 6 patients (range 2.5-10 years).

### **3.3 Conclusions**

Of the 42 pediatric cases of neuropsychiatric events reviewed, we did not find any cases of delirium with impulsive, injurious behavior. There are no labeling recommendations at this time.

## **4. Flumadine (rimantadine)**

### **4.1 Background**

Rimantadine is approved in the U.S. for the treatment of influenza A in adults and prophylaxis of influenza A in adults and children. The **PRECAUTIONS** section of the labeling mentions that seizure-like activity was observed during clinical trials in a small number of seizure patients who were not receiving anticonvulsants. Other events from controlled clinical trials include: impairment of concentration, ataxia, somnolence, agitation, and depression, gait abnormality, euphoria, hyperkinesia, tremor, hallucination, confusion, and convulsions.

### **4.2 AERS search results**

A total of 82 domestic reports of neuropsychiatric events were retrieved from the AERS database for rimantadine. The review focused on **4 unduplicated cases** of neuropsychiatric events in pediatric patients (age  $\leq$  21 years). The indication for use of rimantadine was influenza treatment in three patients and influenza prophylaxis in one patient.

This review identified one event of Delirium with impulsive behavior and injury in a 13-year-old male patient. The patient had hyperactivity, wanted to light matches and became psychotic 4 days after initiating rimantadine for influenza. Medical evaluation excluded flu-induced encephalopathy. This pediatric report prompted the review of 52 reports in adult patients, but similar cases were not found. However, two patients (51-year-old female, 42-year-old male), experienced hallucinations and psychotic episodes.

In addition, one pediatric patient had an event categorized as Delirium, delusion, hallucination, or psychosis and another patient had seizures. There was also one neuropsychiatric event in the miscellaneous category, an event of insomnia.

### 4.3 Conclusions

This review identified one pediatric case of Delirium with impulsive behavior and injury following use of rimantadine. There are no labeling recommendations at this time.

### 4.4 Recommendations regarding M2 Inhibitors

Based on the AERS reports reviewed for amantadine and rimantadine, no labeling changes are warranted at this time. We will continue to monitor the post-marketing data for these products and promptly communicate any significant new findings to the division.

## 5. Overall Conclusion and Recommendations

For the neuraminidase inhibitors oseltamivir and zanamivir, there are reports of Delirium with impulsive behavior and injury in patients who recently initiated these products for the treatment of influenza. These cases provide conflicting evidence as to whether these events are drug-related only, disease manifestation alone, or a combination of drug-disease expression. Although there is still uncertainty about the cause of the reported abnormal behavior, it seems prudent for the labeling for both products to contain language about postmarketing reports of hallucinations, delirium, and abnormal behavior in the **PRECAUTIONS** section. Both labels should have a statement that patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period. Since fatalities have occurred with oseltamivir, the oseltamivir labeling should describe the abrupt onset of the events and state that fatalities have occurred in adult and pediatric patients in Japan and that monitoring is particularly important in pediatric patients in the first day after initiating TAMIFLU. No restrictions in use in the U.S. seem warranted for either neuraminidase inhibitor at this time.

The proposed language for oseltamivir labeling is listed below:

#### **PRECAUTIONS**

***Neuropsychiatric Events:** There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. In some cases, these behaviors have resulted in serious injuries including death in adult and pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior to prevent serious injuries throughout the treatment period with TAMIFLU. Monitoring is particularly important in pediatric patients in the first day after initiating TAMIFLU. If patients develop abnormal behaviors, their healthcare provider should be contacted immediately.*

Based on the AERS reports reviewed for amantadine and rimantadine, no labeling changes are recommended. We will continue to monitor post-marketing reports of neuropsychiatric events for all products approved for influenza treatment and prophylaxis. We will promptly communicate any significant findings from post-marketing sources to the Division of Antiviral Products (DAVP).

## I. Neuropsychiatric Cases with Tamiflu® (oseltamivir)

### 1 Background

Oseltamivir is an oral neuraminidase inhibitor approved for the treatment and prophylaxis of influenza in adults and children 1 year of age or older. The **PRECAUTIONS** section of the U.S. label for Tamiflu® was updated in November 2006 to include post-marketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza and emphasize the need to monitor these patients. In March 2007 the Japanese Ministry of Health, Labor, and Welfare (MHLW) restricted the use of oseltamivir in patients 10-19 years. There was an increase in adverse event reports for oseltamivir following the update to the U.S. label in the fall of 2006 and the restriction in use in Japan in the winter of 2006- 2007. The Pediatric Advisory Committee in November 2005 requested that we conduct a comprehensive review of neuropsychiatric events for oseltamivir for two additional flu seasons (2005-2006 and 2006-2007).

### 2 Product Labeling for Tamiflu (oseltamivir)

#### **CLINICAL PHARMACOLOGY**

**Pharmacokinetics: Absorption and Bioavailability:** Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure after oral dosing.

#### **Elimination**

Absorbed oseltamivir is primarily (>90%) eliminated by conversion to oseltamivir carboxylate. Plasma concentrations of oseltamivir declined with a half-life of 1 to 3 hours in most subjects after oral administration. Oseltamivir carboxylate is not further metabolized and is eliminated in the urine. Plasma concentrations of oseltamivir carboxylate declined with a half-life of 6 to 10 hours in most subjects after oral administration. Oseltamivir carboxylate is eliminated entirely (>99%) by renal excretion.

**Pediatric Patients:** The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in a single dose pharmacokinetic study in pediatric patients aged 5 to 16 years (n=18) and in a small number of pediatric patients aged 3 to 12 years (n=5) enrolled in a clinical trial. Younger pediatric patients cleared both the prodrug and the active metabolite faster than adult patients resulting in a lower exposure for a given mg/kg dose. For oseltamivir carboxylate, apparent total clearance decreases linearly with increasing age (up to 12 years). The pharmacokinetics of oseltamivir in pediatric patients over 12 years of age are similar to those in adult patients.

The **PRECAUTIONS** section states the following:

#### ***Neuropsychiatric Events***

There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period.

**ADVERSE REACTIONS/Observed During Clinical Practice:** syncope and seizures

### 3 Methods/Search Criteria

- Database: FDA’s postmarketing Adverse Event Reporting System (AERS)
- Search date: U.S. marketing approval (October 27, 1999) to May 31, 2007
- Drug: Tamiflu® (oseltamivir)
- Broad Search Strategy encompassing 51 High Level Terms (HLTs) (detailed in Appendix 1 Search Criteria). Also, a separate search was conducted for the HLT Visual Disorders Not Elsewhere Classified (NEC) to retrieve any reports of visual hallucinations coded as “visual disorder.”

### 4 Case Definition

There are multiple obstacles to adequately assessing a clear relationship of neuropsychiatric events to the use of oseltamivir. First, the majority of the reports reviewed were foreign making it difficult to capture an accurate description of an adverse event because of the discrepancies associated with the direct translation of medical events. Second, the MedDRA coding of the adverse events is not consistent among the foreign reports because they are subject to the choice of words from different translators. Third, many events such as convulsions, delirium, and depressed level of consciousness are complications of viral encephalitis secondary to influenza making it difficult to distinguish between complications of the virus, potential adverse effects of oseltamivir, or a combination of both.

In order to provide some level of consistency in the assessment of these cases, the narrative for each of the cases was manually reviewed and the cases were grouped into the following **nine** categories according to the primary neuropsychiatric event described in the narratives from each case. These categories were developed specifically for this case series. These categories are similar to those used in previous reviews, but the categories have been refined for this review.

- **ANX** – Anxiety/fear without hallucinations
- **DIB** – Delirium w/ impulsive behavior & injury
- **DEL** – Delirium, delusion, hallucination, psychosis
- **DLC** – Depressed level of consciousness (from lethargy to coma)
- **LOC** – Loss of consciousness, including syncope
- **MSC** – Miscellaneous
- **PAN** – Panic attacks, panic disorder
- **SUI** – Suicidal events (including ideation)
- **SZ** – Seizures, convulsions

For cases involving events from more than one category, a judgment was made regarding the category which best described the report.

### 5 AERS Results

Prior to the 2005-2006 flu season, AERS was receiving approximately 50 reports of neuropsychiatric events per flu season, but this increased greatly beginning with the 2005-2006 flu season (see Figure 1) and was most notable in pediatric patients (see Figure 2). According to previously completed reviews,<sup>2, 3, 4</sup> the majority of reports about

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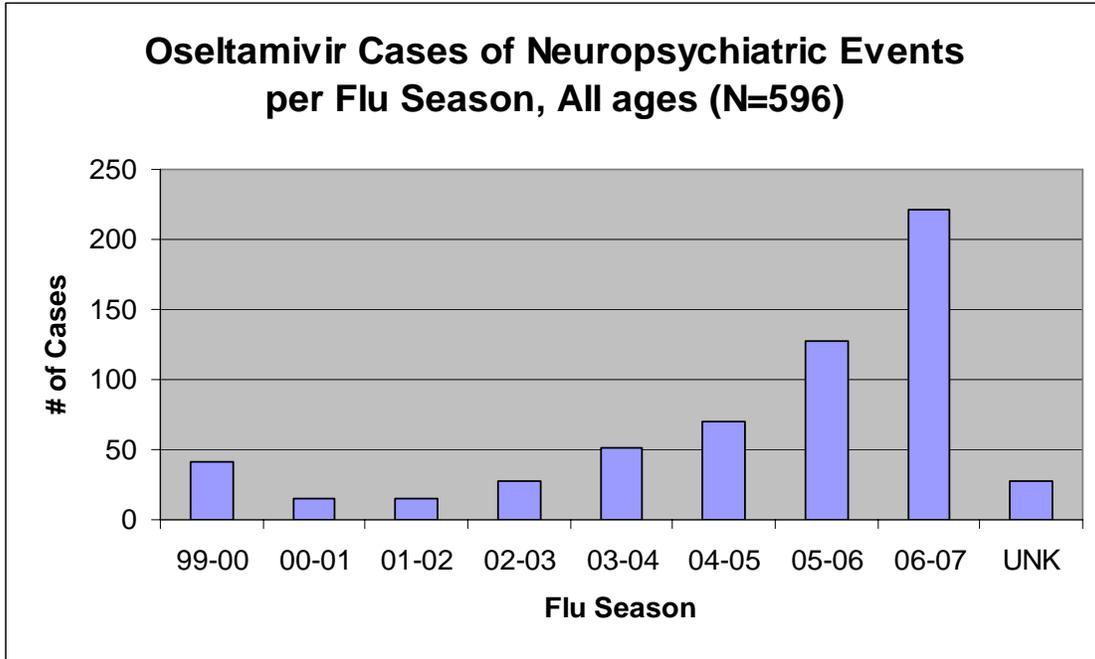
<sup>2</sup> PID D060309 Edwards ET, Truffa MM, Mosholder AD, 09/20/06.

<sup>3</sup> D050502 Edwards ET, Truffa MM, 12/16/05.

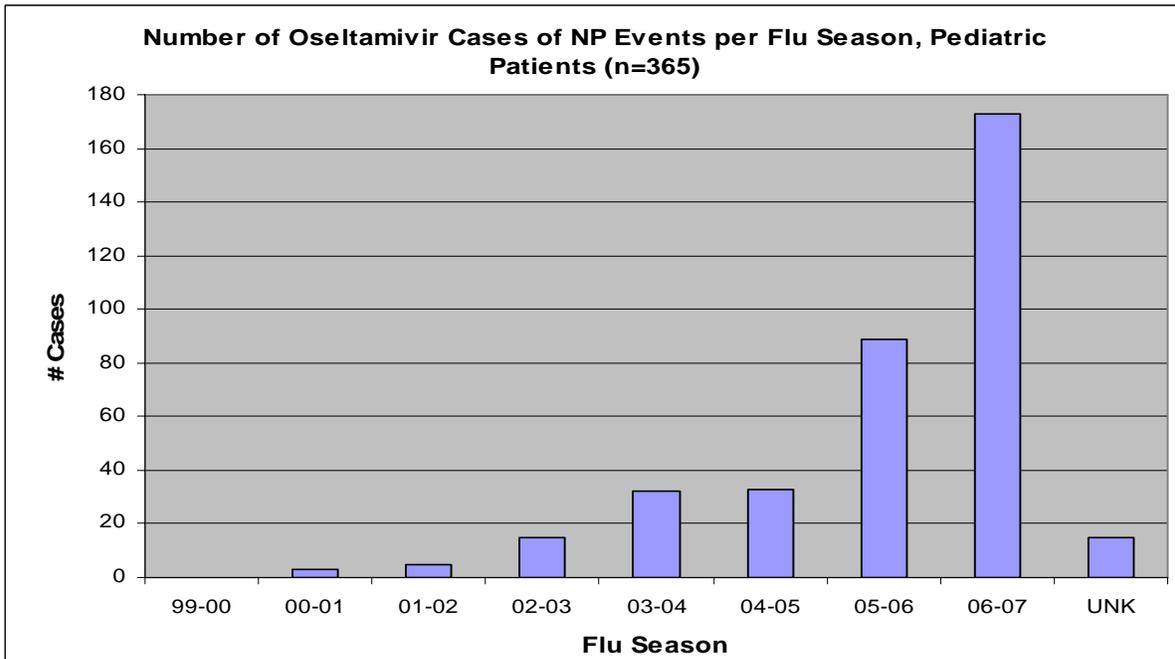
<sup>4</sup> D040223 Edwards ET, Truffa MM, 08/24/05.

neuropsychiatric events were from Japan, primarily in pediatric patients receiving oseltamivir for treatment of influenza. The only reported fatalities from neuropsychiatric events were in Japanese patients.

**Figure 1. Neuropsychiatric Events per Flu Season for Oseltamivir (All ages; received from U.S. marketing approval through 5/31/2007)**



**Figure 2. Neuropsychiatric Events per Flu Season for Oseltamivir (pediatric patients (<math>\leq 21</math> years); received from U.S. marketing approval through 5/31/2007)**



There were 728 AERS reports received during the specified time period (U.S. marketing approval to 5/31/07) that met the criteria for the broad search strategy. Thirty-two duplicate

reports were identified, 10 reports were received after 05/31/07, and 116 reports were excluded because the reports did not include a neuropsychiatric event of interest. **After exclusions there were a total of 596 cases with neuropsychiatric events.**

The narrative for each of the 596 cases was manually reviewed and the cases were placed into the 9 categories of neuropsychiatric events developed for this review and described above.

Additional case characteristics compiled from a manual review of each report include: indication for oseltamivir use, flu season, latency (time and number of doses from oseltamivir initiation to event onset), time to event resolution, presence or absence of fever at the time of event onset, whether or not oseltamivir was discontinued, whether or not the event reoccurred, whether the event resolved, pertinent diagnostic or lab test results and patient race, as available.

The majority of these 596 cases occurred in patients  $\leq 21$  years of age (61%) and were from Japan (75%). The events tended to occur soon after initiation of oseltamivir with a median of 1 or 2 doses (median of 24 hours). The events resolved quickly, within a median of 6 hours.

Of particular note are reports categorized as Delirium with impulsive behavior and self-injury (DIB) [n=59] and Delirium/Delusions/Hallucinations/Psychosis (DEL) [n= 225] that account for 48% of all neuropsychiatric reports in AERS for oseltamivir. There were 5 reports of delirium in pediatric patients that resulted in a fatal outcome; all occurred in Japan. In the remaining reports of Delirium with impulsive behavior and injury, many narratives described similar events of patients attempting to flee or escape by windows or balconies. Or, patients became aggressive or violent and/or performed acts that were injurious to themselves (e.g. banging head against wall) or others (e.g. child tried to strangle mother). In addition, there were 3 reports of completed suicide in adult patients, including one report of a patient that had fallen to their death which was classified by the coroner as an "open verdict."

The clinical characteristics of neuropsychiatric cases following the use of oseltamivir are presented below in Table 1 (all ages) and Table 2 (pediatric patients,  $\leq 21$  years of age). As compared with patients of any age, pediatric patients reported more fever at event onset (41% vs. 30%). Pediatric patients also had shorter latency to event onset, with a median of 3 hours vs. 6 hours (median 1 dose vs. 1 or 2 doses), as compared with patients of any age. Neuropsychiatric events in pediatric patients resolved quicker as well (median 3 hours vs. 6 hours). The miscellaneous category of neuropsychiatric events for patients of all ages included mostly reports of insomnia (N=23), abnormal behavior (N=9), and night terrors (N=8). For pediatric patients, the miscellaneous category was primarily comprised of abnormal behavior (N=7), night terrors (N=7) and unusual speech (N=5).

**Table 1: Clinical Characteristics of Unique Neuropsychiatric Cases for Tamiflu® (oseltamivir) (All ages; received from U.S. marketing approval through 5/31/2007)**

<b>Number of Cases</b>	<b>N= 596</b>						
<b>Age</b>	0 to 12 yrs: 242	Range: 3 months to 94 years					
	13 to 21 yrs: 122	Median: 14 years					
	> 21 yrs: 202	Average: 25.6 years					
	Unknown: 30	≤ 21 yrs of age: 61.2%					
<b>Gender</b>	Male: 335	Unknown: 14					
	Female: 247						
<b>Source/Flu Season</b>	Japan: 444	1999-00: 41	2004-05: 70				
	US: 130	2000-01: 15	2005-06: 127				
	Other: 22	2001-02: 15	2006-07: 221				
		2002-03: 28	Unknown: 28				
		2003-04: 51					
<b>Outcome</b>	Death: 16	Disability: 11					
	Life-threatening: 58	Required Intervention: 5					
	Hospitalization: 187	Medically significant: 337					
<b>Indication for Use/Influenza Type</b>	Treatment of influenza: 529	Influenza A: 200					
	Prophylaxis†: 19	Influenza B: 99					
	Unspecified indication: 48						
<b>Latency (time to onset of symptoms from initiation of treatment)</b>	<u>Doses (n= 526)</u>	<u>Time in hours (n= 520):</u>					
	Range: 1 to 11 doses	Range: 10 seconds to 10 days					
	Median: 1 or 2 doses	Median: 24 hrs					
	Average: 2.6 doses	Average: 32 hrs					
	After 1 <sup>st</sup> or 2 <sup>nd</sup> dose of oseltamivir: 366						
<b>Rechallenge/Dechallenge</b>	Positive Dechallenge: 53	Cont. drug without reoccurrence: 43					
	Negative Rechallenge: 3	AE reoccurred after multiple doses: 45					
<b>Drug Discontinued After Event ‡</b>	Yes: 352	‡39 reports had events that occurred in patients who had already stopped/completed oseltamivir (events occurred within 72 hours of the last dose).					
	No: 57						
	Not stated: 148						
<b>Event resolved (yes/no/not stated/"improved")</b>	Yes: 433	<u>Time to Resolution (n=379)</u>					
	No: 31	Range: seconds to 6 months					
	Not stated: 122	Median: 6 hours					
	"Improved": 10	Average: 2.7 days					
<b>Concomitant Fever at onset of event</b>	Yes: 181 (30.4%)	Yes & No (event recurred): 11 (1.8%)					
	No: 118 (19.8%)	Not stated: 286 (48%)					
<b>Categories of Neuropsychiatric Events by age</b>		<b>Pediatric (≤ 21 years)</b>			<b>Adult (&gt; 21 years)</b>	<b>Age Unk.</b>	<b>Grand Total</b>
		<b>&lt; 1</b>	<b>1-12</b>	<b>13- 21</b>			
<b>ANX</b> - Anxiety/fear without hallucinations		--	1	1	5	2	<b>9</b>
<b>DIB</b> -Delirium w/ impulsive behavior & injury		--	23	25	11	--	<b>59</b>
<b>DEL</b> -Delirium, delusion, hallucination, psychosis		--	134	41	46	4	<b>225</b>
<b>DEL + SZ</b>		--	4	1	--	--	<b>5</b>
<b>DLC</b> - Depressed level of consciousness (from lethargy to coma)		--	9	8	17	1	<b>35</b>
<b>LOC</b> - Loss of consciousness, incl. syncope		1	9	9	31	--	<b>50</b>
<b>MSC**</b> - Miscellaneous		--	26	17	47	20	<b>110</b>
<b>PAN</b> - Panic attacks, panic disorder		--	--	2	4	1	<b>7</b>
<b>SUI</b> - Suicidal events (incl. ideation)		--	1	2	9	--	<b>12</b>
<b>SZ</b> - Seizures, convulsions		4	30	16	31	2	<b>83</b>
<b>SZ + DLC</b>		--	--	--	1	--	<b>1</b>
<b>Grand Total</b>		<b>5</b>	<b>242</b>	<b>122</b>	<b>202</b>	<b>30</b>	<b>596</b>

\*\* **Miscellaneous category** includes the following most commonly reported events: insomnia (23), abnormal behavior not otherwise specified (9), night terrors (8), unusual speech (5), agitation (5), confusion (5), somnolence (4), amnesia (4), dizziness (3), excitement (3), myoclonus (3), sleep walking (2), and insomnia with agitation (2).

† **Prophylaxis cases:** 1 case reported hallucinations and psychosis, but the case was confounded (See section 8).

**Table 2: Clinical Characteristics of Unique Neuropsychiatric Cases for Tamiflu® (oseltamivir) (Pediatric patients < 21 years; received from U.S. marketing approval through 5/31/2007)**

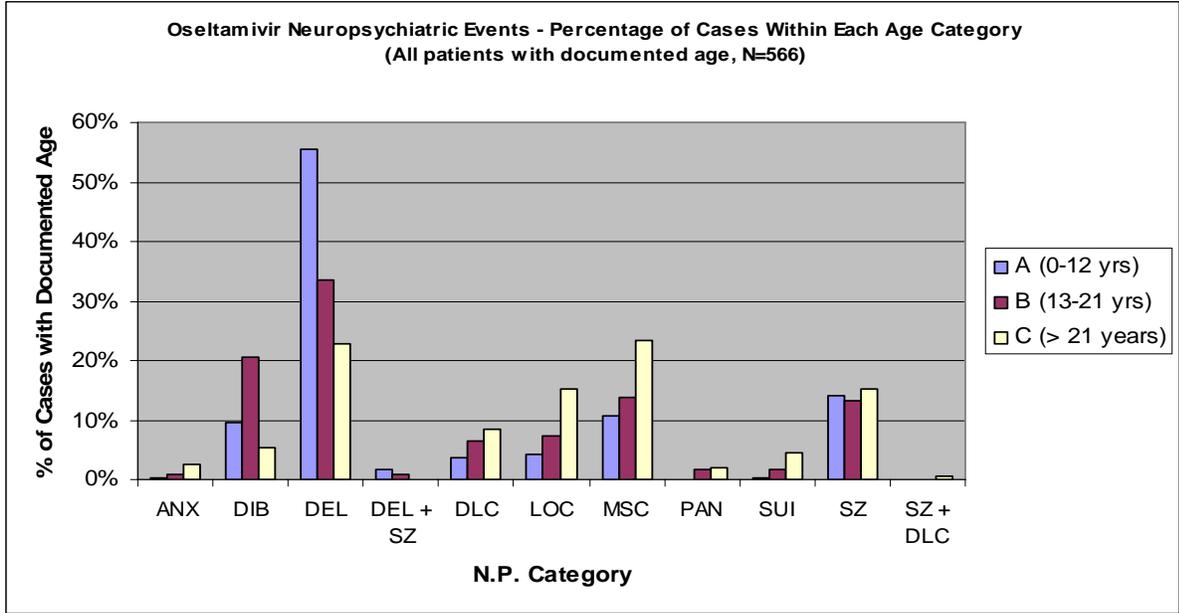
Number of Cases	N= 365					
<b>Age</b>	0 to 12 yrs: 242	Range: 3 months to 21 years				
	13 to 21 yrs: 122	Median: 10 years				
	Unknown: 1	Average: 10 years				
<b>Gender</b>	Male: 241	Unknown: 3				
	Female: 121					
<b>Source/Flu Season</b>	Japan: 316	1999-00: 0	2004-05: 33			
	US: 47	2000-01: 3	2005-06: 89			
	Other: 2	2001-02: 5	2006-07: 173			
		2002-03: 15	Unknown: 15			
		2003-04: 32				
<b>Outcome</b>	Death: 6	Disability: 5				
	Life-threatening: 42	Required Intervention: 0				
	Hospitalization: 113	Medically significant: 196				
<b>Indication for Use/Influenza Type</b>	Treatment of influenza: 346	Influenza A: 150				
	Prophylaxis†: 6	Influenza B: 77				
	Unspecified indication: 13					
<b>Latency (time to onset of symptoms from initiation of treatment)</b>	<b>Doses (n= 337)</b>		<b>Time in hours (n= 330):</b>			
	Range: 1 to 10 doses		Range: 10 seconds to 9 days			
	Median: 1 dose		Median: 12 hrs			
	Average: 2.2 doses		Average: 25 hrs			
	After 1 <sup>st</sup> or 2 <sup>nd</sup> dose of oseltamivir: 261					
<b>Rechallenge/Dechallenge</b>	Positive Dechallenge: 21	Cont. drug without reoccurrence: 25				
	Negative Rechallenge: 2	AE reoccurred after multiple doses: 25				
<b>Drug Discontinued After Event<sup>‡</sup></b>	Yes: 229	‡ 21 reports had events that occurred in patients who had already stopped/completed oseltamivir (events occurred within 72 hours of the last dose).				
	No: 26					
	Not stated: 89					
<b>Event resolved (yes/no/not stated/"improved")</b>	Yes: 292	<b>Time to Resolution (n=262)</b>				
	No: 17	Range: seconds to 6 months				
	Not stated: 51	Median: 3 hours				
	"Improved": 5	Average: 3 days				
<b>Concomitant Fever at onset of event</b>	Yes: 151 (41.4%)	Yes & No (event recurred): 9 (2.5%)				
	No: 62 (17%)	Not stated: 143 (39.2%)				
<b>Categories of Neuropsychiatric Events by age</b>		<b>Pediatric (≤ 21 years)</b>				<b>Pediatric Grand Total</b>
		< 1	1-12	13- 21	Unk	
<b>ANX</b> - Anxiety/fear without hallucinations		--	1	1	--	<b>2</b>
<b>DIB</b> -Delirium w/ impulsive behavior & injury		--	23	25	--	<b>48</b>
<b>DEL</b> -Delirium, delusion, hallucination, psychosis		--	134	41	1	<b>176</b>
<b>DLC</b> - Depressed level of consciousness (from lethargy to coma)		--	4	1	--	<b>5</b>
<b>LOC</b> – Loss of consciousness, incl. syncope		--	9	8	--	<b>17</b>
<b>MSC**</b> - Miscellaneous		1	9	9	--	<b>19</b>
<b>PAN</b> - Panic attacks, panic disorder		--	26	17	--	<b>43</b>
<b>SUI</b> - Suicidal events (incl. ideation)		--	--	2	--	<b>2</b>
<b>SZ</b> - Seizures, convulsions		--	1	2	--	<b>3</b>
		4	30	16	--	<b>50</b>
<b>Grand Total</b>		<b>5</b>	<b>242</b>	<b>122</b>	<b>1</b>	<b>365</b>

\*\* **Miscellaneous category** includes the following most commonly reported events: abnormal behavior not otherwise specified (7), night terrors (7), unusual speech (5), agitation (3), sleep walking (2).

† **Prophylaxis cases:** 1 case reported hallucinations and psychosis, but the case was confounded (See Section 8).

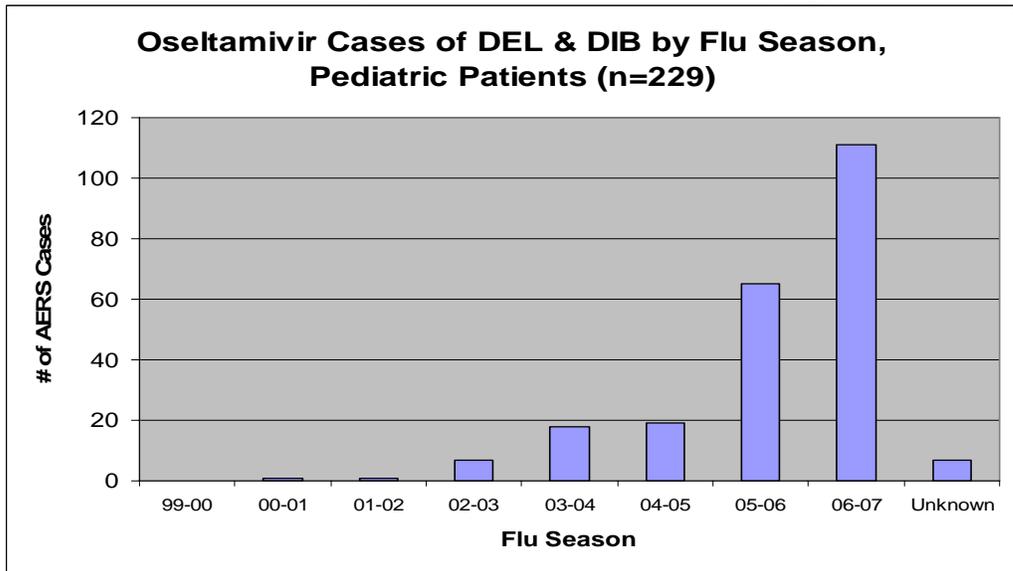
In addition, the neuropsychiatric events for oseltamivir are presented as a percentage of age category Figure 3 below.

**Figure 3. Neuropsychiatric Events Presented by Age Category for Oseltamivir (received from U.S. marketing approval through 5/31/2007)**



Of special interest are the neuropsychiatric events of Delirium with impulsive behavior and injury (DIB) and Delirium, delusion, hallucination, or psychosis (DEL) in pediatric patients. Fatalities associated with these events resulted in a restriction in use in Japan in patients aged 10-19 years beginning in March 2007. Cases of DIB & DEL in pediatric patients are depicted by flu season in the graph that follows (see Figure 4).

**Figure 4. Events of Delirium with impulsive behavior & injury (DIB) and Delirium, delusion, hallucination, psychosis (DEL) per Flu Season for Oseltamivir (Pediatric patients (<=21 years)); received from U.S. marketing approval through 5/31/2007)**



## 6 Neuropsychiatric Events with a Fatal Outcome (n=16): Eight cases potentially related to neuropsychiatric events

Table 3 below summarizes the clinical characteristics of all neuropsychiatric cases with a fatal outcome. The first eight cases are potentially related to neuropsychiatric events, including five adolescent patients who died from injuries suffered from a fall from a high elevation and three adults who completed suicide (two describe suicide by leaping from a high elevation).

The text in the case descriptions in this document was taken from actual AERS reports, and in some cases reflects difficulties in the translation from Japanese to English.

**Table 3: Clinical Characteristics of All Fatal Neuropsychiatric Cases for Tamiflu® (oseltamivir) (received from U.S. marketing approval through 5/31/2007) [N = 16]**

AERS Case Country	Age, gender & flu season	Tamiflu Indication	Time to event onset	Fever at Time of Event	NP Category / Traumatic Injury	Cause of Death
6302858 Japan	14 y/o Female '06-'07	Treatment (B)	3 hours (1 dose)	Unknown	DIB Yes	Fall (cerebral contusion)
While the patient's mother was out grocery shopping, the patient experienced a fatal fall. The apparent fall was from a 1.4-meter high rail in hallway in front of her condo door to the 10th floor to the roof of bike parking lot and then to ground. Patient was found clothed without shoes. She was taken by ambulance to the hospital and declared dead 45 minutes later. The patient was fine 1-2 hours before the incident. No suicide note was found. The patient had a fever of 38.2 degrees 3 hours before the event.						
6252100 Japan	14 y/o Male '06-'07	Treatment (B)	16 hours (2 doses)	Unknown	DIB Yes	Fall (massive head injuries)
In the evening, the patient woke up and complained that he felt ill. Shortly afterward, he told his mother that he was going to the restroom, but instead opened the front door and jumped over 1.26 meter fence and fell 30 meters from 11th floor of his apartment. He was taken to the hospital by ambulance and died 30 minutes later. Local police stated that the possibility that the patient committed suicide is slim, noting that he had no particular trouble and left no suicide note.						
6083411 Japan	12 y/o Male '06-'07	Treatment (unknown)	6 hours (1 dose)	Yes	DIB Yes	Fall (hemorrhage due to a pelvic fracture)
The patient had a fever of almost 40 degrees C in the morning and stayed home from school with his brother. Around 12pm, he took 1 capsule of Tamiflu that had been prescribed for his brother. Around 3pm, acetaminophen was taken because he was still febrile. His brother found just before 6pm that he was gone. There was a call to police that he was lying on the ground in the parking lot of his high-rise apartment building. He was confirmed dead 1 hour later.						
5787263 Japan	14 y/o Male '04-'05	Treatment (A)	2 hours (1 dose)	Unknown	DIB Yes	Fall (hemorrhagic shock)
About 30 minutes after the patient went to his bedroom on the 9 <sup>th</sup> floor of his condominium, the patient was found lying barefoot on the ground in front of his building and later died. No one witnessed the circumstances of the fall and it is not clear whether the patient was having disturbed consciousness or mental disorders at the time of the event. The police said his fingerprints were found on a handrail on the ninth floor of the building and the boy was believed to have fallen after hanging onto the handrail.						
4165603 Japan	17 y/o Male '03-'04	Treatment (A)	2 hours (1 dose)	Unknown	DIB Yes	Traffic Accident (shock caused by traumatic injury)
The patient was instructed to stop amantadine (last administration was in the morning) and start oseltamivir after lunch. Two hours after taking oseltamivir, the patient woke from sleep and ran outside without shoes into the snow. He jumped over a one meter concrete wall, crossing the railroad and over a guard rail of the highway and leaped into the path of a truck. He died of shock caused by traumatic injury of chest.						
6008106 Japan	51 y/o Male '05-'06	Treatment (A)	< 12 hours (1 dose)	Unknown	SUI Yes	Fall (left suicide note)
Oseltamivir was administered at 7pm (only once); no psychiatric or neurological symptoms were observed. At 5 am the next morning, the patient was last seen alive. At 6:30am, it was found that he was not in his bed. He was found dead in the street in front of his 4 <sup>th</sup> floor hospital room. He left a suicide note, but his writing did not suggest the presence of any altered mental status. Before taking oseltamivir, he expressed anxiety about his health and physical condition in the future.						
5996189	44 y/o Male	Treatment	6 days	Unknown	SUI	Fall

AERS Case Country	Age, gender & flu season	Tamiflu Indication	Time to event onset	Fever at Time of Event	NP Category / Traumatic Injury	Cause of Death
Singapore	'05-'06	(Unk)	(10 doses)		Yes	(suicide was an "open verdict")
On the same day as starting oseltamivir, patient had fever of 37.6 degrees. Six days later, the patient committed suicide and died. The suicide was confirmed by an autopsy. The patient had 'fallen to their death' and that an 'open verdict' had been found by a coroner. It was unknown if oseltamivir treatment was ongoing. There did not appear to be any signs of mental problems						
6279565 Japan	45 y/o Male UNK	Treatment (Unk)	1.5 days (3 doses)	Unknown	SUI Unknown	Completed suicide
The wife of the patient reported that he committed suicide after receiving oseltamivir for the treatment of influenza. The patient began treatment with oseltamivir and committed suicide after the third intake of oseltamivir.						
3901374 Japan	61 y/o Male '02-'03	Treatment (Unk)	3 days (6 doses)	Unknown	LOC No	Arrhythmia or cerebral stroke (unconfirmed);
Oseltamivir was started. The next day, the patient's blood sugar level increased. Date unknown: haloperidol and glibenclamide were administered for "a while". Three days after initiating oseltamivir, the patient fell down in the toilet and remained unconscious until he died. The cause of death was suspected to be due to arrhythmia or a cerebral stroke (family refused autopsy). Oseltamivir was maintained up until the time of death.						
3925896 Japan	39 y/o Male '02-'03	Treatment (Unk)	1 day (2 doses)	No	DLC No	Unknown
Patient developed a fever of 38.9 degrees. He had negative rapid influenza test and was prescribed loxoprofen, gatifloxacin and lysozyme chloride. Next day, he returned to physician with persistent fever and had a positive rapid influenza test. Diclofenac and oseltamivir were prescribed. The following day, fever subsided, but he became stuporous in the evening. The patient was transferred to hospital; he was noted to be excited. Diclofenac was stopped. Patient died of unknown reason at the hospital.						
6282054 Japan	57 y/o Male '06-'07	Treatment (A)	6 hours (1 dose)	Yes	SZ No	Pneumonia & convulsion
Approximately 6 hours after initial dose of oseltamivir, the patient had a fever of 39 degrees and experienced a convulsion of the mandible and hands. Blood pressure decreased and dopamine was administered. He continued to have seizures and received diazepam and phenytoin. About 11 hours after oseltamivir administration, the patient experienced a "generalized convulsion" and went into cardiorespiratory arrest. Resuscitation was performed, but the patient died. Cause of death was pneumonia & convulsion (no autopsy performed). Influenza encephalopathy or reaction to oseltamivir was suspected. No findings suggestive of influenza encephalopathy were seen.						
6291821 Japan	39 y/o Male '06-'07	Treatment (Unk)	3 days (6 doses)	Unknown	SZ No	Multiple organ failure and disseminated intravascular coagulopathy (possible herpes encephalitis)
On 3 March (Day 1), the patient had fever of 39 degrees c and visited a nearby hospital and was given oseltamivir for flu prophylaxis. On 5 March (Day 3), the patient felt unwell and drove to the hospital and caused an accident on the way to the hospital. The police questioned him, but he was not able to converse with them. Since he experienced "consciousness disturbed" and convulsion due to "status epilepticus", he was transferred to the hospital by ambulance. Convulsions at arrival, and diazepam was administered for repetitive convulsions, then phenytoin was started. Endotracheal intubation was performed, and he was placed on artificial respiration. Viral encephalitis (herpes encephalitis) was suspected, and acyclovir was started. The patient was sedated for uncontrollable convulsions. On 15 March, pneumonia and atelectasis developed. DIC was diagnosed and continuous heparin was started. On 20 March, MRSA was detected from the sputum, and vancomycin was started. On 24 March, EEG showed spikes (+) and gabapentin was started. On 26 March, the pneumonia progressed into acute respiratory distress syndrome. MOF developed. The infection could not be controlled and died 35 days after starting oseltamivir (no autopsy performed).						
3417696 U.S.A.	83 y/o Male '99-'00	Prophylaxis	2 days (4 doses)	Unknown	SZ No	Unexplained death
On 28 December, the patient experienced weakness, confusion, disorientation, anorexia, incontinence and flu-like symptoms. On 01 January, the patient was admitted to hospital with a temperature of 99.2 and bilateral rales on auscultation. Pneumonia or sepsis suspected; treated with IV fluids, aspirin and ciprofloxacin. The next day, patient commenced oseltamivir; 2 days later ciprofloxacin and oseltamivir were stopped. He was started on ceftriaxone and erythromycin. He was taken for a carotid study, when he suddenly had a seizure which ended spontaneously. Dilantin was given without further seizure activity. Patient was transferred to a nursing home and later died (unexplained death).						
3421843 U.S.A.	76 y/o Female '99-'00	Treatment (Unk)	5 days (10 doses)	Yes	DLC No	Sepsis and cardiovascular collapse
01 January: patient developed a 103-104 degrees fever. 03 January: oseltamivir was started. 06 January: patient's fever was						

AERS Case Country	Age, gender & flu season	Tamiflu Indication	Time to event onset	Fever at Time of Event	NP Category / Traumatic Injury	Cause of Death
103 degrees. 07 January: fever of 104. 08 January: patient was admitted to hospital with altered mental status, fever and possible central nervous system infection. Approximately 3-4 capsules of oseltamivir were unconsumed. 09 January: patient arrested and died. Cause of death was overwhelming sepsis and cardiovascular collapse. She also developed liver and mild renal failure. The patient had experienced streptococcal meningitis, a urinary tract infection and an increased blood myoglobin level.						
3622477 U.S.A.	59 y/o Male '00-'01	Prophylaxis	10 days (11 doses)	No	SZ No	Cerebrovascular accident
The patient was receiving multiple concomitant medications, including Dilantin and Depakote, which were stable and he had not had a seizure for quite some time. On 02 March, the patient started oseltamivir for prophylaxis. On 10 March, the patient was feeling sick and was transferred to hospital. On 12 March, oseltamivir was continuing. The patient died during the morning following a seizure. The patient was afebrile with no acute disease process that could have contributed to the seizure. The cause of death was reported as cerebrovascular accident.						
6241452 U.S.A.	16 y/o Female '06-'07	Treatment (A)	3 days (5 doses)	Yes	MSC (agitation) No	"from becoming sick with the flu"
From a newspaper article: a healthy patient started treatment with oseltamivir twice a day. During the course of the next few days, the patient developed pneumonitis and her general condition worsened with increased cough, chills, fever, lethargy and combativeness. Three days after beginning oseltamivir, the patient was admitted to the hospital. Subsequently, the patient developed disseminated intravascular coagulopathy and expired (approximately 9 days after initiating oseltamivir). The reporting nurse stated that the patient died due to becoming sick with the flu.						

## 7 Rechallenge/ Dechallenge

### 7.1 Negative Rechallenge (n=3) – Representative case presented below.

**Case # 6245962, 5-yr-old female, U.S., 2007:** January 23: cough & fever > 104 for 24 hours. Flu test positive. Patient prescribed oseltamivir. 11 am: patient given a dose of oseltamivir and acetaminophen. 12:30 pm: patient vomited. 2 pm: oseltamivir given. 2:45 pm: patient was very agitated and confused with a temperature of 102. She said "Jo Jo was in her tummy on a board and get the monsters out of here. Make them go away. The monsters are in Daddy and on (her brother). Get the monsters out of here." She looked directly at her mother with very confused and scared and cried "I want my mama. I want my mama." The entire episode lasted for about 3 minutes. Afterwards the patient said, "I just felt funny and weird. I don't like how I feel." Her temperature at this time was about 102 degrees. She had had no other episodes like this again with two subsequent doses of oseltamivir.

### 7.2 Adverse event reoccurred after multiple doses (n=45). Below are 2 representative cases:

**7.2.1 Case# 6266612, 12-yr-old male, Japan, 2007:** Oseltamivir was started for influenza. Ten minutes after administration, he was dazed, and within 30 minutes his sense of distance and height was lost. When he was on a high place, the low place appeared so close that he felt that he would not get injured if he fell. He could not feel how high the bed and the ceiling were. "Visual disturbance" persisted for 11 hours and later disappeared. When another dose of oseltamivir was administered, he was less dazed, but "visual disturbance" occurred again. He lost the sense of distance and became completely unable to see the vertical interval during the time from 30 minutes to 11 hours after taking oseltamivir. He felt a road at 10m upward and a road at 10m downward to be at the same height. He was lying in the bed in twilight state and unable to respond. Although he tried to get up, he did not know where to put his feet because he had lost the sense of up and down. It is inferred that he got the urge to rush out from the veranda because he just wanted to go down (to the road) immediately, rather than he intended to jump down. He returned to the normal state 11 hours after taking oseltamivir. He took the drug 6 times and showed the same symptoms each time.

**7.2.2 Case# 6069442, 6-yr-old female, Japan, 2005:** Patient became slightly loquacious and restless following the first dose of oseltamivir for influenza. She recovered. The second dose of oseltamivir was administered. One or two hours later, she kept talking with a red face and moving around restlessly, which lasted about 2 hours. She recovered when she woke up. The third dose was administered when she was afebrile. Two hours later she was talking to the door, saying "daddy", as if speaking to her father, who was not actually there. She would also climb up the completely dark stairs and did not seem to understand her surroundings. She had not recovered after taking 2-hour nap. She did not remember what she did earlier.

Afterwards oseltamivir was discontinued and the symptoms did not reoccur. The reporter noted that she had taken oseltamivir previously and did not experience any adverse events. This time she took oseltamivir three times, and the symptoms developed within 1-2 hours after each administration. The symptoms did occur when she was afebrile, and the timing of symptoms and the administration of other drugs were not related.

**7.3 Continued therapy with oseltamivir and no reoccurrence of adverse event (n=43). Below are 2 representative cases:**

**7.3.1 Case # 6305113, 14-yr-old female, Japan, 2006:** Patient received oseltamivir for treatment of Influenza A and went to bed. Around 2 hours later, she suddenly got up from sleep and fell off from the window on the second floor while uttering something unspecified. At that time her mother was in her room, but could not stop her since the behavior was so abrupt. The parents found the patient, who hit her back and was sitting in the garden. She looked vacant, but could respond to the family. The event resolved in 10 minutes and she went to bed. The next day her consciousness was completely clear. The event did not recur for the duration therapy with oseltamivir (4 days).

**7.3.2 Case #5749691, 39-yr-old female, France, 2005:** The patient tested positive for flu and with fever (39 degrees C), sore muscles and insomnia. The patient started oseltamivir and within 12 hours experienced visual hallucinations (pages of a book turning over), hypersomnia and an anxiety crisis (fear of death). A clinical examination showed the patient was normal neurologically. The following day, the events of hallucination, torpor, hypersomnia and anxiety crisis resolved. Four days later, oseltamivir was discontinued.

**8 Narratives for Cases of Delirium with Impulsive Behavior and Self Injury in Pediatric Patients (n=48). Below are recent representative pediatric cases.**

**8.1 Case# 6305133, 13-yr-old male, Japan, 2007:** Patient prescribed oseltamivir for influenza B. His mother was instructed not to leave him alone for 24 hours from administration of oseltamivir. He had a fever of 38-39 degrees C at the time of second dose. At midnight about 4 hours after second dose of oseltamivir, he went to his room to sleep (on the 3rd floor of the three-floor house). Between 4:30 am and 5:00 am, he felt like he was having a scary dream where he was being chased by something, and then he suddenly felt that something touched his feet. At that moment he found himself hanging from the edge of a window with his feet on a 10 cm wide protruding part of a concrete roof. Holding the window edge with his arms he managed to climb up and got back to his room. At 5:00 am, he went in to the parents' bedroom noisily and said in terror, "I was almost dead. I was terrified". The parents did not understand his story assuming he was just dreaming. At 7:30 am, the mother noticed the scratches on his forearms, stuff on the lower limbs, and dirt on his soles. She checked his room and noticed that the window was left open, and there were footmarks on the protruding part of the exterior wall. He visited the clinic and he was afebrile, and his general condition was good. He was calm and only said he was scared at that time. He clearly remembered that he went to bed at 12 am and recalled the incidents after he touched the concrete wall on his feet. He knew nothing but felt like he was having a scary dream between these times.

**8.2 Case# 6252118, 15-yr-old male, Japan, 2007:** Oseltamivir was started for influenza B and administered twice. In the afternoon, he felt scared. His temperature was 39 degrees C. He had a nightmare and acted violently, according to the patient. His parents did not see his behavior. Six hours later he acted violently again. He tried to open the front door but failed, and then he went down to the kitchen and returned with a knife. The parents found him putting the knife toward himself in front of the sink, and he dropped the knife. He went to the emergency department and the event resolved in 7 hours. The patient had patchy memory of what he had done and did not remember all the details. He said he had a nightmare.

**8.3 Case# 6298498, 15-yr-old male, Japan 2007:** Oseltamivir was administered for influenza A. Two days later he experienced "abnormal behavior" and almost strangled his mother. Oseltamivir was discontinued. The event resolved in 5-6 hours. The event did not occur after the patient woke from sleep and it was unknown if the patient had a fever at the time of the event.

**8.4 Case# 6298191, 9-yr-old female, Japan, 2007:** Patient was diagnosed with influenza B. At the time of diagnosis, she had a fever of 38.5 degrees C. At 12:30, she took oseltamivir and went to bed. At 12:30 pm on

30 March, she took oseltamivir and went to bed. At 1:00pm, she was heard calling "waa". When a family member went to see her, she was running to the veranda. The family tried to stop her by force, but she shouted "I must go." The family took her to the bathroom by force, where she shouted and used rude words and threw toilet paper with fixed eyes. She settled down in about five minutes, seemingly regaining consciousness and spoke normally. On visit to the hospital at 4:00pm, she was clear in consciousness.

## 9 Cases of Neuropsychiatric Events with Influenza Prophylaxis (n=19)

The indication for use of oseltamivir in the majority of cases in this review was treatment of influenza (n=529). There were only 19 cases with a reported neuropsychiatric event following oseltamivir use for influenza prophylaxis. Table 4 summarizes the reported neuropsychiatric categories and age categories for these 19 prophylaxis cases.

<b>Neuropsychiatric Categories*</b>	<b>A (0-12)</b>	<b>B (13-21)</b>	<b>C (&gt; 21 years)</b>	<b>Grand Total</b>
<b>ANX</b>	--	--	--	--
<b>DIB</b>	--	--	--	--
<b>DEL</b>	--	1	--	<b>1</b>
<b>DLC</b>	--	1	1	<b>2</b>
<b>LOC</b>	1	--	1	<b>2</b>
<b>MSC</b>	1	--	4	<b>5</b>
<b>PAN</b>	--	--	--	--
<b>SUI</b>	--	--	1	<b>1</b>
<b>SZ</b>	1	1	6	<b>8</b>
<b>Grand Total</b>	<b>3</b>	<b>3</b>	<b>13</b>	<b>19</b>

\* **ANX** - Anxiety/fear without hallucinations, **DIB**-Delirium w/ impulsive behavior & injury, **DEL**-Delirium, delusion, hallucination, psychosis, **DLC** - Depressed level of consciousness (from lethargy to coma), **LOC** – Loss of consciousness, incl. syncope, **MSC** - Miscellaneous, **PAN** - Panic attacks, panic disorder, **SUI** - Suicidal events (incl. ideation), **SZ** - Seizures, convulsions

There was one case (**AERS case # 6219652, U.S., 2006**) of psychosis and hallucinations in a patient receiving oseltamivir for influenza prophylaxis. In this case, a 17-year-old male was “not himself” and was confused (“couldn’t follow conversations”) after 4 days of oseltamivir 75mg daily for influenza prophylaxis. The patient was not sleeping and the symptoms progressed to psychosis and paranoia with auditory and visual hallucinations. The patient was admitted to the hospital where a urine drug screen was positive for marijuana and benzodiazepines. There were no cases of Delirium with impulsive behavior and injury.

The 5 cases in the miscellaneous category included: improvement in behavior ("acted like an angel") – 1; confusion – 2; confusion and agitation – 1; and irritability, shortness of breath, constricted feeling around neck, difficulty focusing vision, disoriented – 1.

Seizures occurred in 8 patients, including 3 patients with a prior or current seizure disorder, 1 pediatric patient with a fever of 40 degrees C, and 1 patient receiving a medication known to cause seizures.

**10 U.S. Cases of Neuropsychiatric Events with Oseltamivir Use (n=130). Representative pediatric cases are presented below.**

A total of 130 cases of neuropsychiatric events were reported in U.S. patients (see Table 5 below). The median age of U.S. patients reporting neuropsychiatric events was 28.5 years (range 3 months to 83 years). Pediatric patients comprised 36% of U.S. cases of neuropsychiatric events, including 33 patients (25%) aged 0-12 years and 14 patients (11%) aged 13-21 years.

<b>Table 5: Reported U.S. Neuropsychiatric Events with Tamiflu® (oseltamivir) (received from U.S. marketing approval through 5/31/2007) [N = 130]</b>						
<b>NP Category</b>	<b>0-12 years</b>	<b>13-21 years</b>	<i>Pediatric Total</i>	<b>&gt; 21 years</b>	<b>Unknown Age</b>	<b>Grand Total</b>
ANX	--	--	--	3	2	5
DEL	17	7	24	10	3	37
DIB	2	1	3	1	--	4
DLC	--	--	--	4	1	5
LOC	2	--	2	4	--	6
MSC	5	2	7	24	20	51
PAN	--	1	1	--	--	1
SUI	--	--	--	1	--	1
SZ	7	3	10	9	1	20
<b>Total</b>	<b>33</b>	<b>14</b>	<b>47</b>	<b>56</b>	<b>27</b>	<b>130</b>

Of the 47 cases of neuropsychiatric events in pediatric patients in the U.S., 3 patients experienced Delirium with impulsive behavior and injury. These three cases are described in detail below. In addition, there were 24 U.S. pediatric cases categorized as Delirium, delusion, hallucination, or psychosis (DEL).

**10.1 Case# 6278187, 14-yr-old male, U.S., 2007:** Patient test positive for influenza and took first dose of oseltamivir. Less than 10 minutes later, the patient had an episode of vomiting and expelled most of the medicine. He received a second dose. Just before going to bed administered another dose of oseltamivir. About 1.5 hours later, the father reported that the patient had just awoken from sleep delirious, hallucinating, had run to the window and attempted to jump out. The father reported that his son was "acting crazy" and "ranting", saying things such as "I am going insane, I have to go to a doctor." The episode lasted approximately 15 minutes and patient subsequently calmed down and returned to his normal self. Father said child had been feeling better during the day with no fever prior to going to bed. Because of seriousness of behavior father was advised to take child to ER to be examined and observed for recurrence of behavior and to rule out any other cause for behavior. However, at that time child was back to his normal self, alert, interacting appropriately with no signs of meningismus, photophobia or fever and there was a heavy snowstorm outside, so father opted to observe child at home. He was advised to sleep with child in same room and lock all windows and doors. Child did well overnight with no recurrence of behavior. When examined in the office in the morning, he appeared well with no fever. Physical exam was unremarkable and neurological exam was normal. Patient denied any ingestion of other medicines or substances; father denied having any other medications such as antidepressants, etc. in house. A urine toxicology screen was sent for confirmation.

**10.2 Case# 6172248, 10-yr-old male, U.S., 2006:** In February 2006, the patient went on a week-long cruise to the Bahamas with his family. During the cruise he developed influenza symptoms and was prescribed oral oseltamivir by the cruise physician. The patient took his first dose of oseltamivir and 4-5 hours later experienced delirium manifested by trying to throw lawn chairs overboard and screaming that he needed to find his family. He threw the lawn chairs aside and ran for the cruise ship railing. He later went back to sleep, woke up and walked down the hall, looking for his family. The delirium resolved on the same day and the patient took oseltamivir for two additional days.

**10.3 Case# 6257184, 20-month-old male, U.S., 2007:** The patient started treatment with oseltamivir. About one and a half weeks later, after the patient had taken approximately 6 or 7 doses, he had behavioral changes and night terrors and oseltamivir was discontinued. The mother reported that the patient was afraid of her, ran away from her, and was banging his head against the wall to the point where he probably should wear a helmet. The patient's doctor could not explain his behavior and a neurologist was consulted. At last report, the patient's behavioral changes and night terrors were persisting.

There was one case of a U.S. patient becoming suicidal during treatment with oseltamivir, which is summarized below.

**10.4 Case # 5929190, 40-yr-old male, U.S., 2005:** Patient began to experience severe anxiety attacks after taking the third dose of oseltamivir for treatment of influenza. Patient had a racing heart, and was unable to sleep for more than 15 minute periods. Patient remained in a state of high anxiety, and became suicidal after the seventh dose of oseltamivir. Patient was taken to the emergency room in a suicidal state. Patient stopped taking oseltamivir after the seventh dose, and the anxiety diminished within a week of discontinuing the medication. Prior to taking the medication, the patient had not experienced anxiety attacks.

## 11 Additional Noteworthy Cases of Neuropsychiatric Events

**11.1 Case# 6306649, 23-yr-old male, Japan, 2004:** *Note: case excluded because the patient had not received oseltamivir.* Patient presented with a fever of 38 degrees C and was diagnosed with influenza A. He was prescribed amantadine at 1 tablet twice daily for 3 days, ambroxol hydrochloride, cefcapene pivoxil, rebamipide, and acetaminophen. A pharmacist notified the physician that the patient had been using medications for psychiatric disorders, and amantadine was changed to oseltamivir. Before the administration of oseltamivir, fever was 38 degrees C. He was lying down in a couch while he was waiting to receive the prescribed medications at the pharmacy, and he was sternly rebuked for lying down and looked depressed. Afterward the police reported that the patient fell from the 6th floor of his mansion and that he did not take oseltamivir. Other reported medications were risperidone, cremin, akineton, vegetamin-a, benزالin, carbamazepine and rohypnol. The event outcome was not provided (disability was listed as a serious outcome).

**11.2 Case# 5956430, 7-yr-old male, Japan, 2005:** *Note: oseltamivir therapy changed to amantadine and neuropsychiatric events resolved.* Oseltamivir was started for influenza. Four hours later an antipyretic was administered. Afterwards "abnormal behavior" developed; he could not find bathroom and saw someone who was not there. At the hospital he could answer simple questions, occasionally he spoke nonsensical phrases and could not recognize his mother. Blood test, CT, and MRI found no abnormality, but he was admitted to the hospital. Oseltamivir was switched to amantadine. He showed such "abnormal behavior" as singing a song while kicking in the air; suddenly starting to read out sentences in academic textbooks; and seeing people who were not there. Afterward, consciousness impairment or "abnormal behavior" was not observed, and the fever was subsiding and event resolved.

**11.3 Case # 6305088, 9-yr-old male, Japan, 2007:** *Note: oseltamivir therapy changed to zanamivir and neuropsychiatric events resolved.* A patient with a fever of 39.3 degrees C received oseltamivir for treatment of influenza. During the night, the patient experienced abnormal behavior; he tried to get up and spoke nonsense. The patient reportedly had a fever at the time of the event. Treatment with oseltamivir was discontinued and he was admitted to a hospital. During hospitalization, the patient received zanamivir without any problems. The event reportedly resolved within 8 hours.

**11.4 Case # 6322488, 16-yr-old male, Japan, 2006:** *Note: 6 months later patient had influenza with a high fever and received zanamivir without the occurrence of neuropsychiatric events.* Patient had fever of 40 degrees C, influenza type B was confirmed and oseltamivir was started. About 8 hours later he suddenly got up and dashed outside the house barefoot in his pajamas. He went to the convenience store in his pajamas and came home 10 minutes later. He went back to sleep and was not injured. Next morning, he had a fever of 39 degrees C and he remembered the episode vaguely. The event was reported as resolved on the same day. He received oseltamivir for 4 more days. No abnormal behavior was observed when he had a fever of 39.1 degrees C and received zanamivir for influenza B 6 months later.

**11.5 Case # 3922896, 13-yr-old female, Japan, 2003:** *Note: when the body temperature was between 37 and 38 degrees C, there was no problem taking oseltamivir. Symptoms recurred several months later when receiving*

*diclofenac for fever.* On 23 January, the patient was diagnosed with influenza, and started oseltamivir. The next day, patient's temperature decreased. When the patient was sleeping in afternoon, she suddenly got up and ran to the balcony. Her sister stopped her, but the patient insistently said, "I'm kill myself." When she was sleeping at night, she suddenly got up and ran to the front door. The mother stopped her, at the same time the patient attempted to run and jump out of a window. The patient was refrained and commenced to utter a strange sound. It was reported that when the body temperature was between 37 and 38 C there was no problem taking oseltamivir. On 25 January, the patient continued to utter strange sounds. It was reported that the mother of the patient understood this to be that the patient was delirious from the fever. On 27 January, oseltamivir treatment ceased. The patient visited the clinic and appeared normal, the hallucinations had resolved in 20 to 30 minutes. The reporter stated that the hallucinations appeared when the fever due to influenza began to subside with oseltamivir administration. Several months after oseltamivir treatment for the influenza infection, she received diclofenac 12.5mg because of a fever. Six or seven hours later, she slightly experienced the feelings that she wanted to die, the feelings she had felt during the oseltamivir treatment.

**11.6 Case # 6305113, 14-yr-old female, Japan, 2006:** *Note: direct adult supervision was unable to prevent the impulsive, injurious behavior (previously presented in Section 7.3 describing cases with no recurrence of events during continued oseltamivir).* Patient received oseltamivir for treatment of Influenza A and went to bed. Around 2 hours later, she suddenly got up from sleep and fell off from the window on the second floor while uttering something unspecified. At that time her mother was in her room, but could not stop her since the behavior was so abrupt. The parents found the patient, who hit her back and was sitting in the garden. She looked vacant, but could respond to the family. The event resolved in 10 minutes and she went to bed. The next day her consciousness was completely clear. The event did not recur for the duration therapy with oseltamivir (4 days).

**11.7 Case # 6252100, 14-yr-old male, Japan, 2007:** *Note: direct adult supervision was unable to prevent the impulsive, injurious behavior (previously presented in Table 3. All Fatal Neuropsychiatric Cases).* In the evening, the patient woke up and complained that he felt ill. Shortly afterward, he told his mother that he was going to the restroom, but instead opened the front door and jumped over 1.26 meter fence and fell 30 meters from 11th floor of apartment. He was taken to the hospital by ambulance and died 30 minutes later. Local police stated that the possibility that the patient committed suicide is slim, noting that he had no particular trouble and left no suicide note.

**11.8 Case# 6305133, 13-yr-old male, Japan, 2007:** *Note: direct adult supervision was recommended, but did not prevent the impulsive, injurious behavior (previously presented in Section 8. Reports of Delirium with Impulsive Behavior and Injury).* Patient prescribed oseltamivir for influenza B. His mother was instructed not to leave him alone for 24 hours from administration of oseltamivir because hyperthermia may rarely occur after the administration, leading to a state of excitement or sleepwalking-like symptoms. He had a fever of 38-39 degrees C at the time of second dose. At midnight about 4 hours after second dose of oseltamivir, he went to his room to sleep (on the 3 rd floor of the three-floor house). Between 4:30 am and 5:00 am, he felt like he was having a scary dream where he was being chased by something, and then he suddenly felt that something touched his feet. At that moment he found himself hanging from the edge of a window with his feet on a 10 cm wide protruding part of a concrete roof. Holding the window edge with his arms he managed to climb up and got back to his room. At 5:00 am, he went in to the parents' bedroom noisily and said in terror, "I was almost dead. I was terrified". The parents did not understand his story assuming he was just dreaming. At 7:30 am, the mother noticed the scratches on his forearms, stuff on the lower limbs, and dirt on his soles. She listened to his story again and checked his room and noticed that the window was left open, and there were footmarks on the protruding part of the exterior wall. He visited the clinic. He was afebrile, and his general condition was good. He was calm and only said he was scared at that time. He clearly remembered that he went to bed at 12 am and recalled the incidents after he touched the concrete wall on his feet. He knew nothing but the feeling like he just having a scary dream between these times.

## 12 Concomitant Medications:

Because many patients were receiving additional medications when the neuropsychiatric events occurred, we also examined the classes of medications most commonly prescribed with oseltamivir (see Table 6 below). The names of the co-suspect or concomitant medications were obtained from AERS data listings and the products identified using standard online medical references (e.g. Martindale's Pharmacopeia, AHFS Drug Information, Japanese Pharmacopeia, European Pharmacopeia). This information is presented in summary because it was difficult to

retrieve detailed information about Japanese medications. In addition, the narrative had limited information about the specific formulation, dose(s) administered, and timing relative to the event. In 78% of cases reporting use of an antihistamine, the antihistamine used was considering very sedating. An attempt was made to obtain information about alcohol content of the concomitant medications, but this was not easily or consistently obtained and could not be accurately summarized.

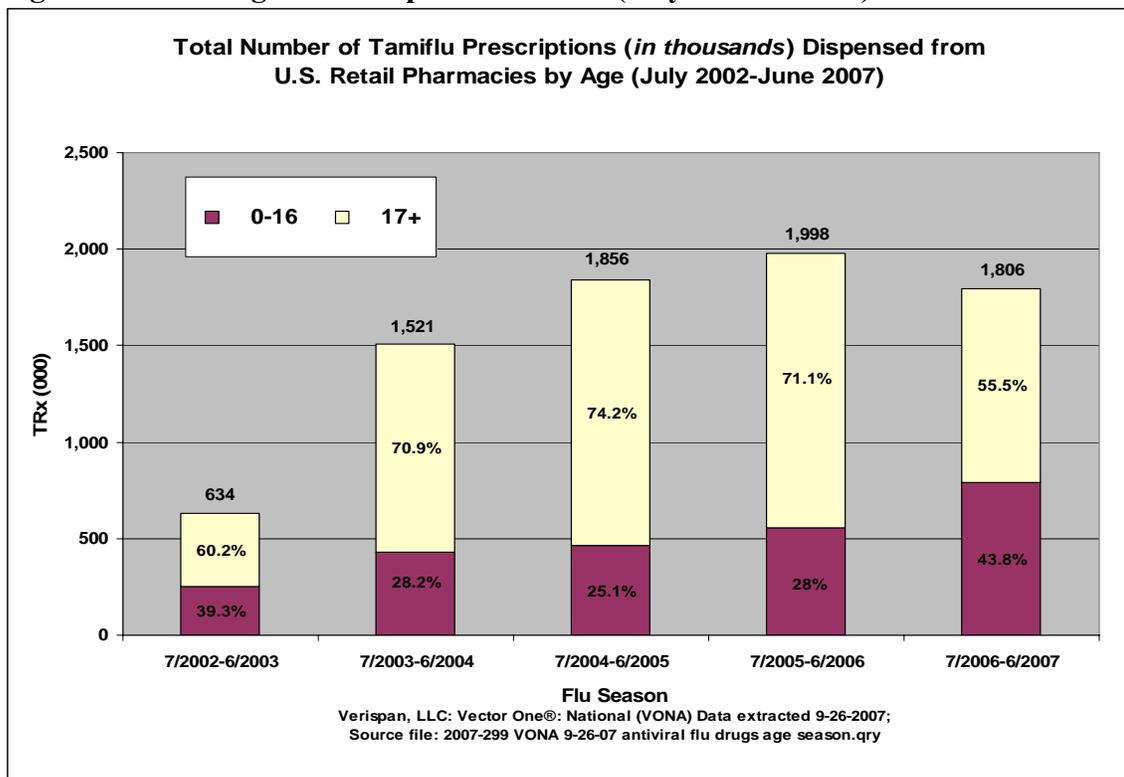
<b>Table 6. Most Commonly Reported Classes of Concomitant Medications for Oseltamivir Events of Delirium with impulsive behavior &amp; injury (DIB) and Delirium, delusion, hallucination, psychosis (DEL) in Pediatric Patients (<math>\leq 21</math> years); received from U.S. marketing approval through 5/31/2007 (N = 229)</b>		
<b>Therapeutic Class</b>	<b># of Cases in AERS</b>	<b>% of Total Pediatric Cases of DIB &amp; DEL</b>
Mucolytic/expectorant	67	29.3%
Antihistamine	59	25.8%
Antitussive	57	24.9%
Antipyretic	57	24.9%
Antibiotic	31	13.5%
Non-steroidal anti-inflammatory drug	16	7.0%
Antiviral	6	2.6%
Dopamine Antagonist	4	1.7%
Hypnotic	3	1.3%

### 13 Discussion

Adverse event reports of neuropsychiatric events for oseltamivir increased in the 2005-2006 flu season and again in the 2006-2007 flu season (see Figures 1, 2 & 4). This increase in reported events may be due to stimulated reporting following the U.S. labeling changes and the media attention following the Pediatric Advisory Committee meeting in November 2006. There was subsequent media attention after the two most recent reports of death from falls in Japanese teenagers that occurred in February 2007 and the Japanese regulators decided in March 2007 to restrict oseltamivir use in patients ages 10-19 yrs of age. Any or all of these factors may have influenced adverse event reporting for neuropsychiatric events with oseltamivir in the U.S. and Japan.

In contrast to the increase in the number of adverse event reports in the last two flu seasons, recent drug use information for oseltamivir shows that overall drug use declined in the U.S., while use in pediatric patients increased (see Figure 5). In Japan, oseltamivir drug use has dramatically decreased for all ages (see Appendix 2, data courtesy of Hoffman-La Roche, Inc.). A detailed summary of drug use in the U.S. for influenza treatment and prophylaxis medications is presented in Appendix 3.

**Figure 5. U.S. Drug Use Data per Flu Season (July 02'-June 07')**



Although the number of post-marketing reports of neuropsychiatric adverse events with oseltamivir have increased in comparison with previous reviews, the clinical characteristics of these cases are very similar to the prior reviews.<sup>2,3,4</sup> However, a major difference is that the AERS database now has reports of abnormal behavior in U.S. patients similar to events previously observed in Japanese patients, although none have been fatal.

A total of 130 cases of neuropsychiatric events were reported in U.S. patients (see Table 5). The median age of U.S. patients reporting neuropsychiatric events was 28.5 years (range 3 months to 83 years), which is slightly older than the median of 14 years for all cases. Pediatric patients comprised 36% of U.S. cases of neuropsychiatric events, including 33 patients (25%) aged 0-12 years and 14 patients (11%) aged 13-21 years. These neuropsychiatric events occurred after a median of 2 doses of oseltamivir and resolved in a median of 24 hours.

It is unknown if the lack of fatal outcomes in the U.S. is due to more severe events occurring in Japanese patients, less overall patient exposure to oseltamivir in the U.S., or due to more effective monitoring of patients in the U.S., as advised in the **PRECAUTIONS** section of the U.S. label. Regardless, the reports of U.S. neuropsychiatric events do not further clarify whether these neuropsychiatric events are due to oseltamivir, influenza, or a combination of both. We cannot determine from this case series if Japanese patients are more susceptible to neuropsychiatric events; however, the U.S. reports demonstrate that these events are not limited to a specific ethnic group, which was unclear at the time of the last review.

We also evaluated the time to event onset after initiation of oseltamivir. The median time from initiation of oseltamivir to event onset was 12 hours, with a median of 1 or 2 doses.

Indeed, 366 of 596 reports (61.4%) stated that the event onset was after the 1<sup>st</sup> or 2<sup>nd</sup> dose of oseltamivir. This suggests a temporal relationship to administration of drug. It could also be argued that fever associated with influenza typically lasts for 2-3 days after onset of symptoms and that these events are disease-related as was demonstrated by the reports of 43 patients that continued therapy with oseltamivir and had no reoccurrence of neuropsychiatric events.

It should also be noted that there are reports that point to potential causes other than the use of oseltamivir, for example fever and influenza. We identified three negative rechallenge cases and cases where the adverse event of interest occurred with the 1<sup>st</sup> or 2<sup>nd</sup> dose while the patient was febrile but did not reoccur with subsequent dosing. Reports were examined to see if continued dosing with oseltamivir was associated with the recurrence or resolution of neuropsychiatric events. In this case series, about an equal number of cases had a recurrence of neuropsychiatric events with continued dosing (N=45) and no subsequent neuropsychiatric events with continuing dosing (N=43). This information does not clarify the role of oseltamivir in the development of neuropsychiatric events.

We looked at a possible association between fever and the reports of abnormal behavior. Although in this case series the presence or absence of fever was not documented in 48% of reports, fever was noted in 30% of reports (41% of pediatric cases). For the cases where the presence or absence of fever was documented (n=310), 58% had a fever at the time of event onset. Twenty-four cases (41%) categorized as Delirium with Impulsive behavior (DIB) were associated with fever at time of event. For the reports categorized as Delirium/Delusions/Hallucinations/Psychosis, 84 of 225 cases (37%) noted fever. These events occurred soon after initiation of oseltamivir, when fever is usually present. It is difficult to make definitive conclusions about a contributory effect of fever with these events because data was missing or poorly documented (e.g. highest temperature, timing to the adverse event). In addition, many of these patients were receiving concomitant antipyretics, making it difficult to interpret this data.

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration and is converted to oseltamivir carboxylate by hepatic esterases. At least 75% of the oral dose reaches systemic circulation as its metabolite, oseltamivir carboxylate. Data from preclinical studies in juvenile rats also found high exposures of oseltamivir and its active metabolite in the brain that is thought to be related to immature blood brain barriers in the very young. For these reasons use of oseltamivir is not recommended for patients less than 1 year of age. There are additional in vitro studies that indicate oseltamivir and its active metabolite have effects on rodent neurons, especially when combined with other agents such as alcohol.<sup>5</sup>

At this point in time, the data are inconclusive about the ability of oseltamivir to cross the blood brain barrier. Roche Pharmaceuticals plans to conduct a sleep study with oseltamivir and will examine electroencephalograms. Electroencephalogram studies should reveal whether or not oseltamivir significantly crosses the blood brain barrier.

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<sup>5</sup> Izumi Y, Tokeda K, O'dell KA, et al. Neuroexcitatory actions of Tamiflu and its carboxylate metabolite. *Neurosci Lett.* 2007 Oct 9;426(1):54-8.

Additional safety information will soon be available for oseltamivir, according to an update provided by the Japanese Ministry of Health, Labour and Welfare (MHLW) on 09/13/07. The MHLW stated that Chugai Pharmaceutical Co, Ltd. will be conducting a sleep laboratory study of oseltamivir (“Phase IV Sleep-related Clinical Study of Tamiflu Capsule in Healthy Adults Volunteers (Male, 20-25 y/o)”). In addition, safety information will also be obtained from an epidemiological survey study of 10,000 cases (approximately 700 medical institutions). The survey will attempt to more precisely examine the time relationship between observed symptoms and drug use, targeting teenage patients (less than 18 years). There is also a national survey in Japan to gather case reports from medical institutions of influenza-associated abnormal behaviors from last flu season and this upcoming flu season. Information from these studies may help to clarify if these neuropsychiatric events are due to oseltamivir, influenza, or a combination of both.

#### **14 Conclusion**

We continue to accumulate postmarketing reports of neuropsychiatric adverse events with oseltamivir and the clinical characteristics of these reports do not differ from previous reviews, except that there are now cases of impulsive, injurious behavior in U.S. patients. There are still no clear-cut cases of neuropsychiatric events when oseltamivir was used for influenza prophylaxis. This current search of AERS identified 596 cases of neuropsychiatric events. The majority of these cases are in patients  $\leq 21$  years of age (61%) and are from Japan (75%). Of particular note are reports categorized as Delirium with impulsive behavior and self-injury (DIB) [n=59] and Delirium / Delusions / Hallucinations / Psychosis (DEL) [n= 225] that account for 48% of all neuropsychiatric reports in AERS for oseltamivir. These events have a short latency (median 24 hours, median of 1 or 2 doses) and are quick to resolve (median of 6 hours). No cases progressed to encephalitis.

There were 5 reports of delirium in pediatric patients that resulted in a fatal outcome. In the remaining reports of delirium with impulsive behavior and self-injury, patients were attempting to flee or escape from windows or balconies and were unsuccessful in their efforts. In addition, there were a few patients who became aggressive or violent and/or performed acts that were injurious to themselves (e.g. banging head against wall) or others (e.g. child tried to strangle mother). In addition, there were 3 reports of completed suicide in adult patients, including one report of a patient that had fallen to their death which was classified by the coroner as an “open verdict.”

Following this comprehensive review, there continues to be uncertainty about whether these events are manifestations of disease, drug-related, or a combination of both. However, the postmarketing data for oseltamivir continue to suggest a possible association between the use of oseltamivir and the development of neuropsychiatric events. The **PRECAUTIONS** section of the U.S. labeling for Tamiflu® currently states the following:

##### ***Neuropsychiatric Events***

*There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period.*

The current labeling does not state that some neuropsychiatric events in Japanese patients have been associated with a fatal outcome.

At this time, we still cannot fully explain the association of “abnormal behavior” observed in the reports following the use of oseltamivir. It is still unclear whether these neuropsychiatric events are drug-related, disease-related, or a combination of drug-disease expression and to date no mechanism of action for these events has been proposed. We cannot rule out the possible contribution of drug to the adverse event over and above the adverse symptoms which may result from the natural history of influenza-illness. Thus, at this time, there is uncertain evidence to definitively state that this is a disease-only process and postmarketing data suggests a possible association between the use of oseltamivir and the development of neuropsychiatric events.

## 15 Recommendations

This comprehensive review of 728 postmarketing reports (596 relevant cases) of neuropsychiatric events did not further clarify whether these events are related to oseltamivir, disease or a combination of drug-disease expression, particularly in pediatric patients. To date there are no fatalities in the U.S. from neuropsychiatric events and there is only one confounded case of psychosis and hallucinations following the use of oseltamivir for influenza prophylaxis.

The **PRECAUTIONS** section of the current U.S. labeling for Tamiflu® notes that self-injury and delirium have occurred, primarily among pediatric patients. Close monitoring of patients is recommended during the treatment period. The current labeling does not state that some events in Japanese patients have been associated with a fatal outcome. We recommend that the **PRECAUTIONS** section on Neuropsychiatric Events be updated to note that some of these neuropsychiatric events in Japanese adult and pediatric patients have resulted in fatalities and the event onset was abrupt. A risk communication strategy (e.g. Prescriber Alert or Public Health Advisory) may be considered to continue to notify prescribers and family members about the need for close monitoring early in treatment with oseltamivir to avoid serious injury from neuropsychiatric events. A restriction on the use of oseltamivir in the U.S. does not seem warranted at this time based on the post-marketing data and the still unanswered question about whether these events are due to oseltamivir, influenza/fever, or a combination of the two. DDRE will continue to closely monitor these types of events and will promptly notify the division if significant new cases are received.

The proposed language for oseltamivir labeling is listed below:

### **PRECAUTIONS**

**Neuropsychiatric Events:** *There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. In some cases, these behaviors have resulted in serious injuries including death in adult and pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior to prevent serious injuries throughout the treatment period with TAMIFLU. Monitoring is particularly important in pediatric patients in the first day after initiating TAMIFLU. If patients develop abnormal behaviors, their healthcare provider should be contacted immediately.*

## II. Neuropsychiatric Cases with Relenza™ (zanamivir)

### 1. Background

Zanamivir is an orally inhaled neuraminidase inhibitor indicated for the treatment and prophylaxis of influenza. Oseltamivir, the other currently marketed neuraminidase inhibitor, has been associated with postmarketing reports of abnormal and self-injurious behavior including reports of deaths in Japanese teenagers from traumatic injuries (e.g. jumping from buildings) after receiving oseltamivir for the treatment of influenza. In March 2007 the Japanese Ministry of Health, Labor, and Welfare (MHLW) requested that the use of oseltamivir in patients 10-19 years be restricted. Soon after this announcement an influx of postmarketing reports of abnormal behavior in Japanese patients using zanamivir for treatment of influenza was noted.

### 2. Product Labeling

#### **CLINICAL PHARMACOLOGY**

**Pharmacokinetics: Absorption and Bioavailability:** Pharmacokinetic studies of orally inhaled zanamivir indicate that approximately 4% to 17% of the inhaled dose is systemically absorbed. The peak serum concentrations ranged from 17 to 142 ng/mL within 1 to 2 hours following a 10-mg dose.

**Elimination:** The serum half-life of zanamivir following administration by oral inhalation ranges from 2.5 to 5.1 hours

**Pediatric Patients:** The pharmacokinetics of zanamivir were evaluated in pediatric patients with signs and symptoms of respiratory illness. Sixteen patients, 6 to 12 years of age, received a single dose of 10-mg zanamivir dry powder via DISKHALER. Five patients had either undetectable zanamivir serum concentrations or had low drug concentrations (8.32 to 10.38 ng/mL) that were not detectable after 1.5 hours. Eleven patients had C<sub>Max</sub> median values of 43 ng/mL (range 15 to 74 ng/mL) and AUC<sub>∞</sub> median values of 167ng/hr/mL (range 58 to 279). Low or undetectable serum concentrations were related to lack of measurable PIFR in individual patients (see **DESCRIPTION, INDICATIONS and USAGE: Description of Clinical Studies and PRECAUTIONS: Pediatric Use**).

#### **INDICATIONS:**

Zanamivir, an influenza neuraminidase inhibitor, is indicated for:

- **Treatment of influenza** in patients 7 years of age and older who have been symptomatic for no more than 2 days
- **Prophylaxis of influenza** in patients 5 years of age and older

**ADVERSE REACTIONS/Observed During Clinical Practice:** syncope and seizures

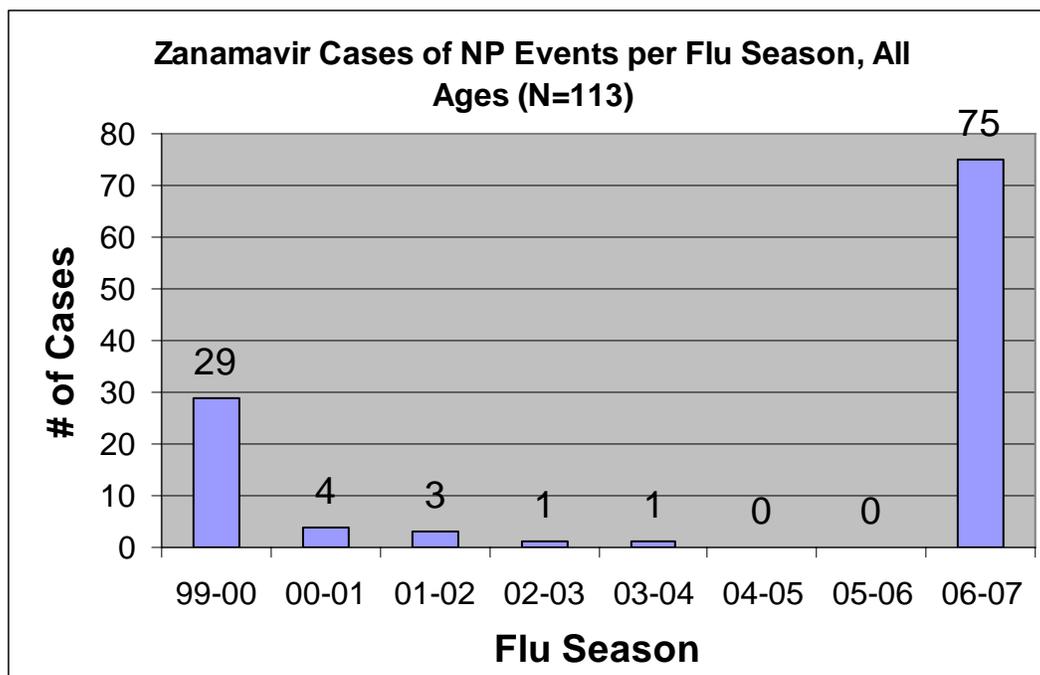
### 3. Methods/Search Criteria

- Search date: U.S. marketing approval (July 26, 1999) to August 1, 2007
- Drug: Relenza™ (zanamivir)
- Combination of 51 HLT from each SOC of Psychiatric Disorders, Nervous System Disorders, and selected PT from SOC Injury, Poisoning and Procedural Complications (see Appendix 1 for details)

#### 4. AERS Results

Prior to January 2007 there were 38 neuropsychiatric reports in AERS spanning 7 years (1999-2006, see Figure 1) with the majority from the first flu season (1999-2000) after zanamivir was marketed in the U.S. The majority of these reports were from the U.S. (74%) and described reports of loss of consciousness (10), seizures (9), and insomnia in adults (5). There are six additional reports describing delirium with hallucinations, but none describing impulsive or self-injurious behavior. Five of these 6 reports are in adults; five are from the US with one from Japan. The U.S. pediatric case involves an 11-year-old female who received inhaled zanamivir to treat influenza and developed hallucinations and dizziness. The patient remained afebrile. Zanamivir was continued and the event remained unresolved. The Japanese case describes visual hallucinations and delirium in a 79-yr-old female. She claimed that "someone was setting the house on fire and a kid was burning and eating snakes". The treating physician commented that the patient's concomitant medications benzyhydrochlorothiazide and fluvoxamine maleate could also induce visual hallucinations.

**Figure 1: Number of Neuropsychiatric Cases with Zanamivir by Influenza Season**



After January 2007, increases in reporting were noted. The sharp increase in the number of postmarketing adverse event reports for zanamivir is probably multi-factorial. Heightened media attention after two deaths from traumatic injuries in Japanese teenagers receiving oseltamivir for the treatment of influenza in February 2007 could have stimulated reporting for zanamivir. As noted above the Japanese regulators changed their product labeling soon after to restrict the use of Tamiflu in patients ages 10-19 yrs of age because they did not feel that the oseltamivir could be safely administered to adolescents and teenagers. This may also have influenced the use of Relenza™ in Japan. Patient exposure to zanamivir in Japan was estimated at 100,000 subjects during the 2005-06 Flu season while 500,000 subjects were exposed during 2006-07. This is a 5-fold increase in exposure of zanamivir over the past two flu season. In the U.S. over the past five

influenza seasons (July 2002 – June 2007) retail dispensed prescriptions for Relenza have decreased substantially (decrease of 75%).<sup>6</sup>

The demographic and clinical characteristics of the zanamivir cases from the 2006-07 influenza season (n=75) appear different than the earlier cases in AERS but are very similar to cases that have been observed with oseltamivir since 2005. For example 70% of cases are from Japan and 64% are in patients  $\leq 21$  yrs of age. Prior to 2007, the majority (76%) of reports were in U.S. adults as compared to 2007 where the majority (92%) of reports are in pediatrics patients from Japan.

There are 166 reports in the AERS database for zanamivir received during the specified time period (U.S. marketing approval to 8/1/07). Six duplicate reports were identified resulting in 160 unduplicated cases. An additional 45 cases were excluded; primarily because the reports do not include a neuropsychiatric event of interest (see Appendix 5 for a list of excluded case numbers). **After exclusions there are a total of 115 cases.**

Please refer to Table 1 for the Clinical Characteristics of Neuropsychiatric Cases with the use of zanamivir in all ages and Table 2 for pediatric patients.

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<sup>6</sup> October 2007 Review of Neuropsychiatric Events and Zanamivir (Relenza™), Courtesy of GlaxoSmithKline.

<b>Table 1: Clinical Characteristics of Unique Neuropsychiatric Cases for Relenza™ (zanamivir) (All Ages; received from U.S. marketing approval (July 26, 1999) through 8/1/2007)</b>						
<b>Number of Cases</b>	<b>N= 115</b>					
<b>Age</b>	0 to 12 yrs – 53 13 to 21 yrs – 21 >21 yrs – 34 Unknown – 7	Range – (5- 79 yrs) Median – 13 yrs Average – 23 yrs (64%) ≤ 21 yrs of age				
<b>Gender</b>	Male – 57 Female – 54 Unknown – 4					
<b>Source/Flu Season</b>	Japan – 81 US – 28 Other* – 6	1999-00 – 29 2000-01 – 4 2001-02 – 3 2002-03 – 1	2003-04 – 1 2004-05 – 0 2005-06 – 0 2006-07- 75			
<b>Outcome</b>	Death – 2 Life-threatening – 4 Hosp – 19 Disability – 1	Required Intervention – 3 Medically significant – 70 Non-serious – 15 Not-Stated – 1				
<b>Indication for Use/Influenza Type</b>	Treatment of influenza – 109 Prophylaxis – 0 Unspecified indication – 6		Influenza A – 23 Influenza B – 20			
<b>Latency (time to onset of symptoms from initiation of treatment)</b>	<u>Doses (n=103):</u> Range (1-14 doses) Median = 1-2 doses Average = 2 doses After 1 <sup>st</sup> or 2 <sup>nd</sup> dose of zanamivir – 75		<u>Time in hours (n= 74)**:</u> Range (10 minutes to 1 week) Median = 12 hrs Average = 24 hrs			
<b>Rechallenge/Dechallenge</b>	<ul style="list-style-type: none"> <li>• Positive Dechallenge</li> <li>• Cont. drug without reoccurrence</li> <li>• AE reoccurred after multiple doses</li> <li>• Negative Rechallenge</li> </ul>		10 14 8 2			
<b>Drug Discontinued After Event</b>	Yes – 62 No – 28 (9 continued therapy for 5 days)					
<b>Event resolved (yes/no/not stated)</b>	Yes – 91 No – 4 “Improved” – 7 Not stated – 13	<u>Time to Resolution (n=49)<sup>‡</sup></u> Range (30 sec to 5 days) Median = 24 hrs Average = 24 hrs				
<b>Concomitant Fever at onset of event</b>	Yes – 52 No – 11 Not stated – 52					
<b>Categories of Neuropsychiatric Events by age</b>		<b>Pediatric (≤21 yrs)</b>		<b>Adults (&gt; 21 yrs)</b>	<b>Age Unknown</b>	<b>Grand Total</b>
		0-12 yrs	13- 21yrs			
<b>ANX</b> -Anxiety, fear without Hallucinations	<b>ANX</b>	0	0	1	0	<b>1</b>
<b>DIB</b> -Delirium w/impulsive behavior & injury	<b>DIB</b>	5	1	1	0	<b>7</b>
<b>DEL</b> -Delirium, delusions, hallucinations, psychosis	<b>DEL</b>	41	13	5	2	<b>61</b>
<b>DLC</b> -Depressed level of consciousness	<b>DLC</b>	2	1	0	0	<b>3</b>
<b>LOC</b> -Loss of consciousness, incl. syncope	<b>LOC</b>	0	2	9	2	<b>13</b>
<b>MSC</b> ∞- Miscellaneous	<b>MSC</b>	3	3	10	2	<b>18</b>
<b>PAN</b> -Panic attacks, panic disorder	<b>PAN</b>	0	0	0	0	<b>0</b>
<b>SUI</b> -Suicidal events (incl. ideation)	<b>SUI</b>	0	0	0	0	<b>0</b>
<b>SZ</b> - Seizures, convulsions	<b>SZ</b>	2	1	8	1	<b>12</b>

\*Germany -2, one each for Belgium, Ireland, France and Spain

\*\* 12 additional cases reported onset of symptoms as “same day”

‡ 11 additional cases reported resolution of symptoms as “same day”

∞ MSC-Miscellaneous category includes the following most commonly reported events: 5- insomnia, 2-nightmares

**Table 2: Clinical Characteristics of Unique Neuropsychiatric Cases for Relenza™ (zanamivir) (Pediatric Patients; received from U.S. marketing approval (July 26, 1999) through 8/1/2007)**

Number of Cases		N= 74		
<b>Age</b>	0 to 12 yrs – 53 13 to 21 yrs – 21	Range – (5- 19 yrs) Median – 11 yrs Average – 10.5 yrs		
<b>Gender</b>	Male – 41 Female – 31 Unknown – 2			
<b>Source/Flu Season</b>	Japan – 71 US – 3	1999-00 – 2 2000-01 – 1 2001-02 – 1 2002-03 – 0	2003-04 – 0 2004-05 – 0 2005-06 – 0 2006-07- 69	
<b>Outcome</b>	Death – 0 Life-threatening – 2 Hosp – 10 Disability – 1	Required Intervention – 1 Medically significant – 59 Non-serious – 1		
<b>Indication for Use/Influenza Type</b>	Treatment of influenza – 71 Prophylaxis – 0 Unspecified indication – 3	Influenza A – 21 Influenza B – 20		
<b>Latency (time to onset of symptoms from initiation of treatment)</b>	<u>Doses (n=68):</u> Range (1-9 doses) Median = 1 doses Average = 2 doses After 1 <sup>st</sup> or 2 <sup>nd</sup> dose of zanamivir – 54	<u>Time in hours (n= 50)*:</u> Range (1hour to 5 days) Median = 9.75 hrs Average = 17 hrs		
<b>Rechallenge/Dechallenge</b>	<ul style="list-style-type: none"> <li>• Positive Dechallenge</li> <li>• Cont. drug without reoccurrence</li> <li>• AE reoccurred after multiple doses</li> <li>• Negative Rechallenge</li> </ul>	4 8 4 2		
<b>Drug Discontinued After Event</b>	Yes – 46 No – 20 (7 continued therapy for 5 days) Not stated – 8			
<b>Event resolved (yes/no/not stated)</b>	Yes – 64 No – 1 “Improved” – 4 Not stated – 5	<u>Time to Resolution (n=24)<sup>‡</sup></u> Range (30 sec to 2 days) Median = 24 hrs Average = 19.8hrs		
<b>Concomitant Fever at onset of event</b>	Yes – 41 No – 10 Not stated – 23			
<b>Categories of Neuropsychiatric Events by age</b>		<b>Pediatric (≤21 yrs)</b>		<b>Pediatric Total</b>
		0-12 yrs	13- 21yrs	
<b>ANX</b> -Anxiety, fear without Hallucinations	<b>ANX</b>	0	0	<b>0</b>
<b>DIB</b> -Delirium w/impulsive behavior & injury	<b>DIB</b>	5	1	<b>6</b>
<b>DEL</b> -Delirium, delusions, hallucinations, psychosis	<b>DEL</b>	41	13	<b>54</b>
<b>DLC</b> -Depressed level of consciousness	<b>DLC</b>	2	1	<b>3</b>
<b>LOC</b> -Loss of consciousness, incl. syncope	<b>LOC</b>	0	2	<b>2</b>
<b>MSC<sup>∞</sup></b> - Miscellaneous	<b>MSC</b>	3	3	<b>6</b>
<b>PAN</b> -Panic attacks, panic disorder	<b>PAN</b>	0	0	<b>0</b>
<b>SUI</b> -Suicidal events (incl. ideation)	<b>SUI</b>	0	0	<b>0</b>
<b>SZ</b> - Seizures, convulsions	<b>SZ</b>	2	1	<b>3</b>

\* 11 additional cases reported onset of symptoms as “same day”

‡ 6 additional cases reported resolution of symptoms as “same day”

∞ MSC-Miscellaneous includes 1- sleep terror, 1-sleep walking, 1-psychomotor movements, 1-agression, 1-excitement with slurred speech and 1 – “encephalopathy like-symptoms”

## 5. Deaths (n=2)

**Neither Death was related to a neuropsychiatric event; both reports are in adults.** One patient died of myocardial infarction 6 months after receiving zanamivir. The second death occurred in a 57-year-old female receiving inhaled zanamivir (Relenza) powder and dipyrone for fever. She developed a fear of death, no feelings in hands and feet. She was hospitalized and hemorrhagic fever was diagnosed. She went into a coma and died due to multiple-organ failure. Laboratory data showed streptococcus pneumonia in blood.

## 6. Rechallenge/Dechallenge

<b>Table 3: Rechallenge/Dechallenge Information for Zanamivir</b>	
	<b>Number of AERS Report</b>
<b>Negative Rechallenge</b>	<b>2</b>
<b>Cont. drug without reoccurrence of adverse event</b>	<b>14</b>
<b>Positive Dechallenge</b>	<b>10</b>
<b>AE reoccurred after each dose with multiple doses</b>	<b>8</b>

The two negative rechallenge cases and the fourteen reports stating that the neuropsychiatric adverse event did not reoccur with continued use of zanamivir do not support a drug-event association. It is more likely that these events are associated with influenza or other concomitant medications than with the use of zanamivir.

However, the positive dechallenge cases and cases in which the reporter indicated that the neuropsychiatric adverse event reoccurred with subsequent doses would support a drug-event association.

*Reviewer Comment: The text in the following case descriptions was taken from the actual AERS reports, and in some cases reflects difficulties in the translation from Japanese to English.*

### **Description of Negative Rechallenge Cases (n=2)**

- **Case # 6291939 11-yr-old male, Japan, 2007:** Approximately one to two hours after starting therapy with zanamivir, patient experienced hallucinations such as saying "someone is there". Body temperature (BT) was of 40 degrees C. Relenza was discontinued and events improved. Two days later BT increased and Relenza was restarted. After reintroduction of zanamivir the events did not recur and treatment with zanamivir was continued for 5 days.
- **Case # 6314663 13-yr-old male, Japan, 2007:** Patient started zanamivir for influenza B infection. At midnight, the patient called his mother to his room and stated that a person from the television had asked him for "5003 yen" and he appeared to be in a daze. Treatment with zanamivir was discontinued. Approximately 2 days later, the patient restarted zanamivir due to persistent fever. The events did not recur, and the patient did not exhibit abnormal behavior, thereafter. Patient had received concomitant medication in the past, but no abnormalities were observed.

## Description of Select Cases where therapy with zanamivir was continued with no reoccurrence of adverse event

- **Case# 6322732, 10-yr-old female, Japan, 2007:** Patient inhaled zanamivir and approximately 90 minutes later experienced abnormal behavior with restlessness and saying "I feel queer". She would not lie down and tried to "hold a blanket and her mother's foot." The patient had a high fever. The next day she still had a high fever (40 degrees C), with clouding of consciousness and inhaled Relenza. Treatment with zanamivir was continued for 3 more days after event resolved.
- **Case# 6336584, 8-yr-old female, Japan, 2007:** The patient with influenza B inhaled zanamivir hydrate for the second time and went to bed. One hour later the patient was sleeping on bed, when she suddenly stood up, looked at the curtain, and started laughing and chuckling. When her mother asked what was going on, she said that she could see Crayon Shin-chan (a comedy animation character) and started laughing again. Her mother reported that this laughter lasted for about 1-2 minutes. After that, the patient went to bed and fell asleep. No abnormality had been observed since then. The patient inhaled zanamivir hydrate for 3 days in total and no abnormality was observed.

## Description of Select Cases of Adverse Event Reoccurring after Multiple Doses

- **Case# 3534790, 49-yr-old female, US, 1999-00:** A nurse practitioner reported that a male received zanamivir for treatment of influenza. After inhaling 2-3 doses of zanamivir, (in the presence of a fever), the patient experienced hallucinations. With his next dose (in the absence of fever), the patient again experienced hallucinations. Each episode resolved quickly. Zanamivir was discontinued after the second episode.
- **Case# 6262400, 10-yr-old female, Japan, 2007:** Two to 3 hours after inhaling Relenza for treatment of influenza B, the patient suddenly talked in delirium, not responding to her mother and in a daze (focusing her eyes on one point in the room). The patient inhaled Relenza three times and a similar episode occurred each time about 2-3 hours after each inhalation. Relenza was discontinued at the discretion of the patient's mother and concomitant medications were continued. The patient did not have a fever when and after inhaling Relenza (acetaminophen had been prescribed as an antipyretic, which was not used at all through the entire course). No events occurred after the discontinuation of zanamivir.
- **Case# 6299804, 10-yr-old male, Japan, 2007:** Patient started a 5-day course of zanamivir and approximately 90 minutes later experienced hallucination such as saying "The curtain is swinging" or "I feel as if I am going to fall sideward", which were also considered as lightheadedness due to pyrexia. Treatment with Zanamivir was continued. Patient again inhaled zanamivir hydrate and experienced abnormal behavior and began to repeatedly go up and down the stairs while counting numbers. His family stopped him doing that, and he went to bed again. After another dose of zanamivir the patient (with persistent fever) had hallucination such as beginning to mutter incomprehensible words; he "grinningly" said that he "gained passing pills and thus would be able to pass". All of the symptoms were observed when pyrexia occurred. Treatment with Relenza was discontinued. Oseltamivir phosphate was started and the patient had no adverse event.

## 7. Description of Cases of Delirium with Impulsive Behavior and Injury (N=7)

**Table 4: Zanamivir Cases of Delirium with Impulsive Behavior and Injury (N=7)**

Case#	Event Year Location	Age (yrs) Sex	Time to Event # Doses	Indication/Fever
6259253	2007 Japan	5 Male	5 hours after 1st dose	Treatment of Influenza A Fever
Abnormal behavior, hallucinations, difficulty speaking and urinary incontinence were noted. The patient said "powdery thing, powdery thing", and uttered other nonsensical phrases. <u>The patient suddenly dashed to the entrance of the house but did not get out.</u> Head CT scan - no abnormalities. Patient returned to normal the next day.				

6262399	2007 Japan	11 Male	1 hour after 1st dose	Treatment of Influenza B fever
1 hour after 1 <sup>st</sup> dose suddenly woke up and said, "I can't find the square thing.", "No, this isn't what I want." <u>He stood up and tried to rush out from the room.</u> "That side is the dream, and this side isn't. I want to go to the dream side." He started to cry such as "What's the matter with my life?" He was very much afraid. Events resolved				
6292914	2007 Japan	11 Male	4 hours after 1 <sup>st</sup> dose	Treatment of Influenza B Fever
Chinese herbal medicine, acetaminophen and Relenza. Patient shouted " <u>My head is spinning.</u> " and " <u>I see no meaning in living.</u> " The patient writhed in torment, she was held down; her whole was head cooled and returned to the normal. <u>Inhaled Relenza again without any subsequent symptoms (no fever).</u> Event resolved.				
6307813	2007 Japan	15 Female	"Soon" after 1 <sup>st</sup> Dose	Treatment of Influenza A Fever
Soon after starting Relenza, felt poorly and stated " <u>I felt like jumping from the roof.</u> " At that time, the patient's body temperature was 38 degrees C. Zanamivir was discontinued and events resolved.				
6286510	2007 Japan	30 Female	2-3 hours after 1 <sup>st</sup> dose	Treatment of Influenza
Pregnant (30 weeks, not certain)/2-3 hours after 1 <sup>st</sup> dose hallucination and began to walk in opposite direction from her house; her husband alerted her and she came back. Apologized by repeatedly bowing to the wall in the bathroom. <u>Later found pounding her head against the wall and was stopped by her family.</u> Treatment with zanamivir was discontinued and the events resolved on the same day. Outcome of the pregnancy unknown.				
6259252	2007 Japan	6 Male	2 hours after 1 <sup>st</sup> dose	Treatment of Influenza A Fever
Suddenly moved around with eyes wide open, shouting, "Yipe!", "I'm scared", "Someone is coming." etc. The patient did not stop moving although his mother held him down. Calmed down in 10-15 minutes. 2.5 hrs after 2 <sup>nd</sup> dose suddenly shouted and moved around. His fever was 39 degrees C. His parents held him down but he kept shouting and tried to move, shouting "I'm scared. I'm scared" and "My chest feels tight".				
6275915	2007 Japan	10 Male	1-1.5 hours after 1 <sup>st</sup> dose	Treatment of Influenza B Fever
40 degrees C fever 30 minutes after inhaling Relenza and shouted one hour later, "I'm scared." Fever of 38.9 degrees C after 2nd inhalation. Suddenly got up and went wild. Relenza was discontinued. Next daytime fever of 38.6 degrees C suddenly ran around in the house, swinging around a toy sword. Later no symptoms with temp of 36+ degrees C.				

**Physician's comments for Case# 6259253:** "Hallucination, abnormal behavior, urinary incontinence and speech disorder definitely related to influenza. The present case seems to be a complication of influenza itself. When a patient has influenza in future, the patient and his/her family should be explained about careful monitoring for 48 hours and the possibility of abnormal behavior associated with influenza, regardless of the use of a drug for influenza. The patient got excited, saw hallucinations and suddenly began to run at the onset of the first episode. The patient headed to the entrance of the house but did not get out of the house, being interrupted by the door. If the patient were bigger and stronger e.g. an elementary school pupil or junior high school student, he would have met a traffic accident or fall down."

**Physician's comment Case# 6292914:** "In reality, the event occurred four hours after the second inhalation; and the subsequent three inhalations were not associated with any symptom (the patient inhaled Relenza in a state where the fever was going down). Given the above course, the event was considered a symptom caused by high fever associated with influenza itself. As the parent reported, the patient tried to drop down through the window from the second floor, saying, "Let me die." This episode confirms a risk that children in his/her teens may have suicidal thoughts when having an influenza-related fever. The physician requests GSK to caution against this risk to all people concerned."

**Patient's parent's comment Case# 6292914:** "Parent was surprised since the patient said weird things suggestive of suicidal wishes such as "Let me die.", "My head is spinning and it makes me feel sick.", "Please throw me down through the window." The patient unsuccessfully tried to get up but just managed to move her limbs. The parent thought that the patient's symptom was just like what was reported on TV."

## 8. Discussion

The recent postmarketing reports of neuropsychiatric adverse events with zanamivir and oseltamivir particularly the reports of delirium and abnormal behavior raise additional questions about the safety profile of neuraminidase inhibitors, both individually and as a class: 1) are the neuropsychiatric adverse events a drug-related class effect that has emerged with increased use of zanamivir in Japan over the last two influenza seasons, 2) are these events primarily a manifestation of influenza with limited contribution from neuraminidase inhibitor(s), or 3) are these events caused by a combination of drug-disease expression.

Although zanamivir and oseltamivir are both neuraminidase inhibitors, they have very different routes of administration and systemic absorption. Oseltamivir is a tablet that is readily absorbed from the gastrointestinal tract after oral administration and is converted to oseltamivir carboxylate by hepatic esterases. At least 75% of the oral dose reaches systemic circulation as its metabolite, oseltamivir carboxylate. By comparison, only 4% to 17% of the orally inhaled dose of zanamivir is systemically absorbed and to date, there is no data on human CSF concentrations of zanamivir. GSK provides further data on the pharmacokinetics of zanamivir<sup>6</sup>: “Most of the zanamivir after inhaled administration is largely deposited in the oropharynx (77.6%) and the lungs (13.2%). Due to poor bioavailability, systemic exposure to zanamivir is low (4-17%). No information on the actual CNS concentrations achieved after inhalational or intravenous administration in humans is available. Whole body autoradiography studies following administration of radiolabelled zanamivir in rats (intratracheal and intravenous) and dog (intravenous) demonstrate the lowest or no exposure in the brain of the animals, which is consistent with the highly polar nature of the drug. Given the low systemic exposure of oral inhaled zanamivir, it is expected that CNS exposure of zanamivir would be low to none. Because of this, it is unlikely zanamivir, administered at the labeled inhalational dose, and could result in a direct toxic effect within the CNS.” Based on these data we believe it is unlikely that zanamivir has substantial penetration into the CNS.

Besides the low potential if zanamivir to penetrate the CNS, there is other evidence from the postmarketing reports that points to potential causes other than the use of zanamivir for the neuropsychiatric adverse events, for example fever and influenza. We identified two negative rechallenge cases and cases where the adverse event of interest occurred with the 1<sup>st</sup> or 2<sup>nd</sup> dose while the patient was febrile but did not reoccur with subsequent dosing. There are also reports of patients completing a 5-day course of therapy without further complications after the initial event resolved suggesting that the adverse event was more closely associated with the acute phase of influenza rather than with drug.

We looked at a possible association between fever and the reports of abnormal behavior. Six of the 7 cases (86%) that we categorized as Delirium with Impulsive Behavior and Injury (DIB) were associated with fever at time of event. For the reports categorized as Delirium/ Delusions/ Hallucinations/ Psychosis, 32 of 61 cases (52%) noted fever. However, 38% percent of the DIB cases did not include information on fever at the time of the adverse event. When examining the cases with available data on fever (n=44), 86% had a concomitant fever around the time of the event. It is difficult to make definitive conclusions about a contributory effect of fever because of missing data and data that does specifically state that the patient had a fever at the exact onset of the adverse event. Many of these patients also received concomitant antipyretics.

There is also evidence to support a possible drug-event association. The unusual characteristics of these adverse events are different from the more commonly recognized central nervous system symptoms related to influenza that are not encephalitis or encephalopathy. Delirium has been associated with high fever, but patients with influenza-induced fever are usually described as listless and irritable not hyperactive or self-injurious. Unlike the reports of delirium with abnormal and self-injurious behavior that have been reported with oseltamivir and now zanamivir.

An evaluation of time to onset of event to after initiation of therapy with zanamivir noted a median time to onset of 12 hours. The median number of doses was 1-2 doses with 75 of 115 cases stating that the onset of the event occurred after the 1<sup>st</sup> or 2<sup>nd</sup> dose of zanamivir suggesting a temporal relationship to administration of drug. It could also be argued that fever associated with influenza typically lasts for 2-3 days after onset of symptoms and that these events are influenza-related as was demonstrated by the reports of 14 patients that continued therapy with zanamivir with no reoccurrence of the adverse event.

## 9. Conclusions

We have received 115 postmarketing cases of neuropsychiatric adverse events with zanamivir; 74 (64%) in patients  $\leq$  21 years of age and 81 (70%) from Japan. Ninety-five percent of patients used zanamivir for the treatment of influenza at the time of the adverse event; there are no reports with prophylaxis use. Many of these reports share the same characteristics as the reports we have previously reviewed with oseltamivir. However, there are no reports of fatalities in pediatric patients from traumatic injuries sustained from “jumping or falling” from buildings. We categorized 7 reports as Delirium with Impulsive Behavior and Injury in which the patient expressed “fear” and attempted to flee or expressed a desire to “jump,” but ultimately did not result in serious injury or death.

Review of the available data regarding the neuropsychiatric adverse events with zanamivir provides conflicting evidence as to whether these events are drug-related only, disease manifestation alone, or a combination of drug-disease expression. The pharmacokinetic profile of zanamivir with its a low potential to penetrate into the CNS and cases where the adverse event of interest occurred with the 1<sup>st</sup> or 2<sup>nd</sup> dose while the patient was febrile but did not reoccur with subsequent dosing suggest that these neuropsychiatric events are a manifestation of influenza alone. However, other data including the reoccurrence of neuropsychiatric events after each dose for multiple doses and postmarketing reports of hallucinations prior 2007 support a potential drug-event association.

At this time, we still cannot fully explain the association of “abnormal behavior” observed in the reports to the use of zanamivir. It is still unclear whether these neuropsychiatric events are drug-related only, disease manifestation alone, or a combination of drug-disease expression and to date no mechanism of action for these events has been proposed. On balance, we feel the propensity of the evidence favors an influenza-induced etiology, however, we cannot rule out the possible contribution of drug to the adverse consequence over and above the adverse symptoms which may result from the natural history of influenza-illness.

## 10. Recommendations

Despite of the uncertainty around the potential cause of the reported abnormal behavior and the contribution of zanamivir; it still seems prudent at this time to caution prescribers and patients about these adverse events observed in patients treated with zanamivir. Hallucinations, delirium, and abnormal behavior are currently unlabeled events for zanamivir. We recommend adding a statement describing the postmarketing reports of hallucinations, delirium, and abnormal behavior that have been observed in patients receiving zanamivir for the treatment of influenza to the Relenza™ product label under **PRECAUTIONS**. We also recommend including a statement that patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period with zanamivir.

### III. Neuropsychiatric Cases with Symmetrel® (amantadine hydrochloride)

#### 1. RELEVANT SYMMETREL (AMANTADINE HYDROCHLORIDE, USP) LABELING (5/03) FOR NEUROPSYCHIATRIC ADVERSE EVENTS

##### WARNINGS

**Deaths:** Deaths have been reported from overdose with SYMMETREL. Acute toxicity may be attributable to the anticholinergic effects of amantadine. Drug overdose has resulted in cardiac, respiratory, renal or central nervous system toxicity.

**Suicide Attempts:** Suicide attempts, some of which have been fatal, have been reported in patients treated with SYMMETREL, many of whom received short courses for influenza treatment or prophylaxis. Patients who attempt suicide may exhibit abnormal mental states which include disorientation, confusion, depression, personality changes, agitation, aggressive behavior, hallucinations, paranoia, other psychotic reactions, and somnolence or insomnia.

**CNS Effects:** Patients with a history of epilepsy or other “seizures” should be observed closely for possible increased seizure activity.

##### ADVERSE REACTIONS

Less frequently (1-5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, somnolence, nervousness, dream abnormality, agitation. Infrequently (0.1-1%) occurring adverse reactions are: psychosis, slurred speech, euphoria, thinking abnormality, amnesia, hyperkinesia. Rare (less than 0.1%) occurring adverse reactions are: convulsion, suicidal attempt, suicide, and suicidal ideation (see WARNINGS).

Other adverse reactions reported during postmarketing experience with SYMMETREL usage include:

**Nervous System/Psychiatric** - coma, stupor, delirium, delusions, aggressive behavior, paranoid reaction, manic reaction. Abrupt discontinuation may also precipitate delirium, agitation, delusions, hallucinations, paranoid reaction, stupor, anxiety, depression and slurred speech;

#### 2 Methods/Search Criteria:

**Search Type:**  AERS     Literature     Other

**Search Date:** July 30, 2007

**Drug Name:** Symmetrel® (amantadine hydrochloride)

**MedDRA Terms:** see Appendix 1

#### 3. AERS Results

There were 840 reports for patients of all ages of neuropsychiatric adverse events associated with the use of Symmetrel (amantadine hydrochloride) using the search criteria listed above.

We further selected 69 pediatric reports from patients ranging in age from 1 – 21 years in order to find out whether there are any similarities to cases of neuropsychiatric adverse events observed with the use of Tamiflu. We are particularly interested in cases of Delirium with impulsive behavior and injury. All 69 reports were manually reviewed; 68 unduplicated cases were identified.

A total of 26 cases were excluded from further review for the various reasons (see Appendix 2). The remaining **42** unduplicated cases were reviewed, and the clinical characteristics are summarized in Table 1.

<b>Table 1: Clinical Characteristics of Unique Neuropsychiatric Cases for Symmetrel® (amantadine) (Pediatric Patients ≤ 21 years; received from U.S. marketing approval through July 30, 2007)</b>																						
<b>Number of Cases</b>	<b>N= 42</b>																					
<b>Age</b>	0 to 12 yrs – 27 13 to 21 yrs – 15	Range – (2.5- 20 yrs) Median – 11 yrs Average – 11 yrs																				
<b>Gender</b>	Male – 21 Female – 19 Unknown – 2																					
<b>Source/Flu Season</b>	US – 41 Canada – 1																					
<b>Outcome</b>	Death – 0 Hosp – 16 Required Intervention – 2	Medically significant – 19 Not stated – 1																				
<b>Indication for Use</b>	Treatment of influenza – 28 Prophylaxis – 6 Other indication – 8	Influenza A – 4 Influenza B – 0 Not stated – 38																				
<b>Latency (time to onset of symptoms from initiation of treatment)</b>	<u>Doses (n=36):</u> Range (1 dose -365 days) Median = 5 days After 1 <sup>st</sup> dose of amantadine – 6																					
<b>Rechallenge/Dechallenge</b>	Event Resolved	29																				
	AE reoccurred after multiple doses	2																				
<b>Categories of Neuropsychiatric Events by age</b>	<table border="1"> <thead> <tr> <th></th> <th><b>Pediatric Total</b></th> </tr> </thead> <tbody> <tr> <td><b>ANX</b></td> <td><b>3</b></td> </tr> <tr> <td><b>DIB</b></td> <td><b>0</b></td> </tr> <tr> <td><b>DEL</b></td> <td><b>18</b></td> </tr> <tr> <td><b>DLC</b></td> <td><b>7</b></td> </tr> <tr> <td><b>LOC</b></td> <td><b>0</b></td> </tr> <tr> <td><b>MSC</b></td> <td><b>4</b></td> </tr> <tr> <td><b>PAN</b></td> <td><b>0</b></td> </tr> <tr> <td><b>SUI</b></td> <td><b>3</b></td> </tr> <tr> <td><b>SZ</b></td> <td><b>7</b></td> </tr> </tbody> </table>			<b>Pediatric Total</b>	<b>ANX</b>	<b>3</b>	<b>DIB</b>	<b>0</b>	<b>DEL</b>	<b>18</b>	<b>DLC</b>	<b>7</b>	<b>LOC</b>	<b>0</b>	<b>MSC</b>	<b>4</b>	<b>PAN</b>	<b>0</b>	<b>SUI</b>	<b>3</b>	<b>SZ</b>	<b>7</b>
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<u><b>ANX</b></u> -Anxiety, fear without Hallucinations																						
<u><b>DIB</b></u> -Delirium w/impulsive behavior & injury																						
<u><b>DEL</b></u> -Delirium, delusions, hallucinations, psychosis																						
<u><b>DLC</b></u> -Depressed level of consciousness																						
<u><b>LOC</b></u> -Loss of consciousness, incl. syncope																						
<u><b>MSC</b></u> - Miscellaneous																						
<u><b>PAN</b></u> -Panic attacks, panic disorder																						
<u><b>SUI</b></u> -Suicidal events (incl. ideation)																						
<u><b>SZ</b></u> - Seizures, convulsions																						

#### 4 Discussion

The amantadine label includes **WARNINGS** for central nervous system (CNS) effects, suicide attempts, and death from overdose. With respect to biological plausibility for CNS effects, it should be noted that amantadine is also indicated for Parkinson’s Disease, so clearly, the drug has pharmacological activity in the CNS.

We did not identify any pediatric patients experiencing Delirium with impulsive behavior and injury in this case series for amantadine. There are three reports of Suicidal events with intentional ingestion. These patients are 17, 18 and 19 years old, respectively. The majority of the patients exhibited Delirium, delusions, hallucinations, psychosis (Category DEL, n = 18) or depressed level of consciousness (category DLC, n = 7). There are two patients who experienced confusion and hallucination reported with body temperature of 102 and 104 degrees Fahrenheit; the high fever could also be contributing to the adverse events. Convulsions occurred in younger population with age ranging from 3 to 12 years. Two distinctive adverse events were observed in patients treated

with amantadine that have also been observed with oseltamivir; “fear” and “nightmares” were reported in six patients in the younger age group of 2.5 to 10 years.

## **5 Conclusions**

Of the 34 patients treated with amantadine either for influenza treatment or prophylaxis and the eight patients with other indications, we did not find any cases with similar abnormal behavior as was observed in patients exhibiting delirium with impulsive behavior and self-injurious behavior during the use of oseltamivir.

The current labeling for Symmetrel<sup>®</sup> (amantadine) contains adequate language describing the CNS effects, suicide attempts and deaths that have occurred with the use of amantadine. We do not have any additional labeling recommendation at this time.

## IV. Neuropsychiatric Cases with Flumadine® (rimantadine hydrochloride)

### 1. RELEVANT FLUMADINE® (RIMANTADINE HYDROCHLORIDE, USP) LABELING (6/06) FOR NEUROPSYCHIATRIC ADVERSE EVENTS

**PRECAUTIONS: GENERAL:** In clinical trials of Flumadine, the occurrence of seizure-like activity was observed in a small number of patients with a history of seizures who were not receiving anticonvulsant medication while taking Flumadine.

**ADVERSE REACTIONS:** Adverse events reported most frequently (1-3%) at the recommended dose in controlled clinical trials: insomnia, nervousness. Less frequent adverse events (0.3 to 1%): impairment of concentration, somnolence, agitation, depression. *Additional adverse events (less than 0.3%) reported at recommended doses in controlled clinical trials were: Nervous System:* gait abnormality, euphoria, hyperkinesia, tremor, hallucination, confusion, convulsions. In addition to the adverse events reported above, the following were also reported at higher than recommended doses: agitation

Adverse Reactions in trials of rimantadine and amantadine: in a six-week prophylaxis study of 436 healthy adults reported with an incidence >1 %: nervousness, impaired concentration, depression

**GERIATRIC USE:** Geriatric subjects experienced considerably more central nervous system and gastrointestinal adverse events than comparable geriatric subjects receiving placebo. Central nervous system events including dizziness, headache, anxiety, asthenia, and fatigue, occurred up to two times more often in subjects treated with rimantadine than in those treated with placebo.

**OVERDOSAGE:** Overdoses of a related drug, amantadine, have been reported with adverse reactions consisting of agitation, hallucinations, cardiac arrhythmia and death.

### 2 Methods/Search Criteria:

**Search Date:** July 30, 2007

**Drug Name:** Flumadine® (rimantadine hydrochloride)

**MedDRA Terms:** see Appendix 1

### 3. AERS Results

There were 82 domestic reports for patients of all ages of neuropsychiatric adverse events associated with the use of Flumadine (rimantadine hydrochloride) using the search criteria listed above. All 82 reports were manually reviewed, and 60 unduplicated reports were identified.

We further selected eight reports from pediatric patients ranging in age from 1 – 21 years in order to find out whether there are any similarities to cases of neuropsychiatric adverse events observed with the use of Tamiflu. We are specifically interested in cases of Delirium with impulsive behavior and injury.

Four cases were excluded from the review because two patients [AERS cases #5412395 (5M), 3296768 (16M)] had a medical history of seizure disorder, mental retardation, or Angelman's syndrome; these patients also were taking concomitant anticonvulsants, and antidepressants. One 20-year-old male patient [AERS Case # 345999] experienced 10 episodes of syncope after taking two doses of Flumadine and Zithromax; he was diagnosed with third degree heart block which is a labeled adverse event under ADVERSE REACTIONS section of the current labeling. One 13-year-old female patient [AERS Case # 5119439] who was given Flumadine for influenza prophylaxis; she took 10-12 tablets of Flumadine in an attempt to commit suicide due to quarrel with her boyfriend. These two later patients did not experienced CNS symptoms.

The remaining 4 unduplicated cases were reviewed for this consult, and the clinical characteristics are summarized in Table 1.

<b>Table 1: Clinical Characteristics of Unique Neuropsychiatric Cases for Flumadine® (rimantadine) (Pediatric Patients; received from U.S. marketing approval through July 30, 2007)</b>		
<b>Number of Cases</b>	<b>N= 4</b>	
<b>Age</b>	0 to 12 yrs – 1 13 to 21 yrs – 3 Range – (6-19 yrs)	
<b>Gender</b>	Male – 4 and Female – 0	
<b>Source/Flu Season</b>	US – 4	
<b>Outcome</b>	Death-0, Hosp-1, Medically significant-2, not stated-1	
<b>Indication for Use</b>	Treatment of influenza – 3 Prophylaxis – 1	Influenza A – 1 Influenza B – 0
<b>Latency (time to onset of symptoms from initiation of treatment)</b>	Range (1 dose -6 days) Median = 1.5 days After 1 <sup>st</sup> dose of amantadine – 0	
<b>Rechallenge/Dechallenge</b>	Event Resolved	3
	AE reoccurred after multiple doses	1
<b>Categories of Neuropsychiatric Events by age</b>	<b>DIB</b> -Delirium w/impulsive behavior & injury - 1 <b>DEL</b> -Delirium, delusions, hallucinations, psychosis-1 <b>SZ</b> - Seizures, convulsions -1 <b>MSC</b> Miscellaneous-1	

#### 4 Discussion

Flumadine® (rimantadine) label includes **PRECAUTIONS**, and **ADVERSE REACTIONS** sections listing central nervous system (CNS) effects such as seizures, insomnia, dizziness, nervousness, and hallucinations that are similar to the events exhibited in the four pediatric patients we have evaluated.

Of the four pediatric patients treated with rimantadine either for influenza treatment or prophylaxis, we observed one case of Delirium with impulsive behavior and injury. A 13-year-old male patient [AERS Case # 3621758] experienced hyperactivity that became psychotic four days after starting Flumadine for influenza. He was evaluated by a neurologist who reported that there was no flu-induced encephalopathy. A urine drug screen revealed no relevant information. The reporter, a pediatrician, stated that the mother said that she had to watch her son because he wanted to light matches.

We reviewed an additional 52 reports involving patients over 21 years old to investigate if other patient experienced similar delirium with impulsive and self-injurious behavior as the adolescent described above. We have not found any similar cases.

However, we did find patients with other neuropsychiatric events. Two patients [AERS cases # 3514180 (51F) and 5119444 (42M)] experienced hallucinations and psychotic episodes; the reports did not provide detailed descriptions of either adverse events. Three patients experienced anxiety and nervousness. Five patients had depressed level of consciousness with one 47-year-old male patient [AERS case #3433075] received a 2-week course of sparfloxacin a month before he developed flu-like symptoms. He started Cipro for 2 days with no improvement and replaced with a course of Bactrim on 12/30/99. He reportedly had taken Flumadine for one day (date unknown). On 1/5/00, he felt worse and visited the ER; he was hospitalized after experiencing a cardiac arrest

while in the ER and later receiving dialysis and was comatose. This patient had abnormal laboratory values including markedly elevated liver enzymes, hyperkalemia, leukocytosis, elevated INR and prothrombin time. The last update reported that this patient may receive a liver transplant. One 47-year-old female patient [AERS case # 5353418] experienced syncope: the patient took a single tablet of Flumadine 100mg before retiring; she woke up about 5am the next morning, felt nauseous and vomited. A short time thereafter, while standing, she felt weak and passed out. She recovered after receiving treatment at ER. Eleven patients experienced convulsions. Fourteen patients experienced insomnia, dizziness, confusion, disorientation and other adverse events. Lastly, 16 reports were excluded with the similar reasons as for the pediatric group.

## **5 Conclusions**

The current labeling for Flumadine® (rimantadine) contains information on CNS effects, but, does not specifically include information on Delirium with impulsive behavior and injury as described in the case above. We have only one report of a pediatric patient who experienced possible impulsive and self-injurious abnormal behavior among the 60 domestic cases reviewed. At this time we do not recommend any changes to the rimantadine label. However, we will continue to closely monitor these neuropsychiatric events and promptly communicate any new findings to DAVP.

## APPENDIX 1. Search Criteria

### NEUROPSYCHIATRIC SEARCH CRITERIA

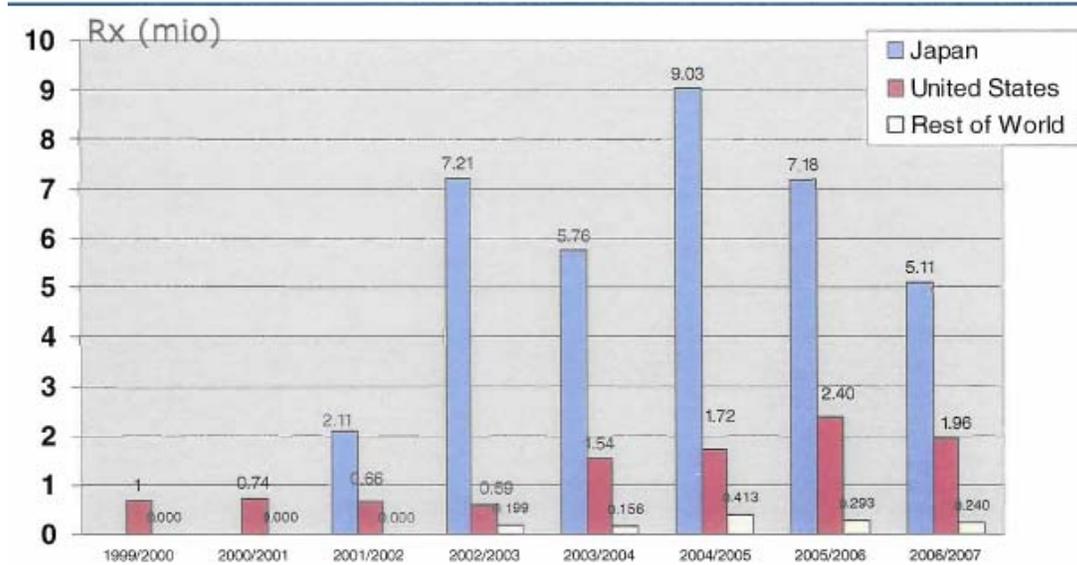
The AERS database was searched using a total of 51 MedDRA High Level Terms (HLTs) selected from the System Organ Class (SOC) Psychiatric Disorders, SOC Nervous System Disorders, and SOC Injury, Poisoning and Procedural Complications.

- *SOC Psychiatric Disorders*
  - HLGT Anxiety disorders and symptoms
    - 1. HLT **Anxiety disorders NEC (incl obsessive compulsive disorder)**
    - 2. HLT **Anxiety symptoms**
    - 3. HLT **Fear symptoms**
    - 4. HLT **Panic symptoms**
  - HLGT Changes in physical activity
    - 5. HLT **Increased physical activity levels**
  - HLGT Cognitive and attention disorders and disturbances
    - 6. HLT **Attention deficit and disruptive behaviour disorders**
    - 7. HLT **Specific cognitive ability disturbances**
  - HLGT Communication disorders and disturbances
    - 8. HLT **Communications disorders**
    - 9. HLT **Speech and language usage disturbances**
  - HLGT Deliria (incl confusion)
    - 10. HLT **Confusion and disorientation**
    - 11. HLT **Deliria**
  - HLGT Depressed mood disorders and disturbances
    - 12. HLT **Mood alterations with depressive symptoms**
  - HLGT Disturbances in thinking and perception
    - 13. HLT **Delusional symptoms**
    - 14. HLT **Perception disturbances**
    - 15. HLT **Thinking disturbances**
  - HLGT Impulse control disorders NEC
    - 16. HLT **Impulse control disorders**
  - HLGT Mood disorders and disturbances NEC
    - 17. HLT **Affect alterations NEC**
    - 18. HLT **Emotional and mood disturbances NEC**
    - 19. HLT **Mood disorders NEC**
  - HLGT Personality disorders and disturbances in behaviour
    - 20. HLT **Behaviour and socialisation disturbances**
    - 21. HLT **Personality disorders NEC**
  - HLGT Psychiatric and behavioural symptoms NEC
    - 22. HLT **Abnormal behaviour NEC**
    - 23. HLT **Psychiatric symptoms NEC**
  - HLGT Sleep disorders and disturbances
    - 24. HLT **Disturbances in initiating and maintaining sleep**
    - 25. HLT **Dyssomnias**
    - 26. HLT **Parasomnias**
    - 27. HLT **Sleep disorders NEC**
    - 28. HLT **Sleep disorders due to general medical condition**

- HLGT Suicidal and self-injurious behaviours NEC
  - 29. HLT **Suicidal and self-injurious behaviour**
- *SOC Nervous system disorders*
  - HLGT Central nervous system infections and inflammations
    - 30. HLT **Encephalitis NEC**
    - 31. HLT **Encephalitis of viral origin**
  - a. HLGT Central nervous system vascular disorders
    - 32. HLT **Traumatic central nervous system haemorrhages**
    - 33. HLT **Central nervous system vascular disorders**
  - HLGT Encephalopathies
    - 34. HLT **Encephalopathies NEC**
    - 35. HLT **Encephalopathies toxic and metabolic**
  - HLGT Mental impairment disorders
    - 36. HLT **Memory loss (excl dementia)**
    - 37. HLT **Mental impairment (excl dementia and memory loss)**
  - HLGT Movement disorders (incl Parkinsonism)
    - 48. HLT **Paralysis and paresis (excl cranial nerve)**
  - HLGT Neurological disorders NEC
    - 39. HLT **Disturbances in consciousness NEC**
    - 40. HLT **Speech and language abnormalities**
    - 41. HLT **Coma states**
    - 42. HLT **Cortical dysfunction NEC**
  - HLGT Neurological disorders of the eye
    - 43. HLT *Neurologic visual problems NEC*
  - HLGT Seizures (incl subtypes)
    - 44. HLT **Generalised tonic-clonic seizures**
    - 45. HLT **Seizures and seizure disorders NEC**
    - 46. HLT **Absence seizures**
    - 47. HLT **Partial complex seizures**
  - HLGT Sleep disturbances (incl subtypes)
    - 48. HLT **Abnormal sleep-related events**
  - HLGT Structural brain disorders
    - 49. HLT **Structural brain disorders NEC**
- *SOC Injury, poisoning and procedural complications*
  - HLGT Injuries NEC
    - 50. HLT Non-site specific injuries NEC (including only the following 6 PT)
      - PT **Accident**
      - PT **Accident at home**
      - PT **Fall**
      - PT **Injury**
      - PT **Road traffic accident**
      - PT **Self mutilation**
  - HLGT Bone and joint injuries
    - 51. HLT **Fractures and dislocations NEC**

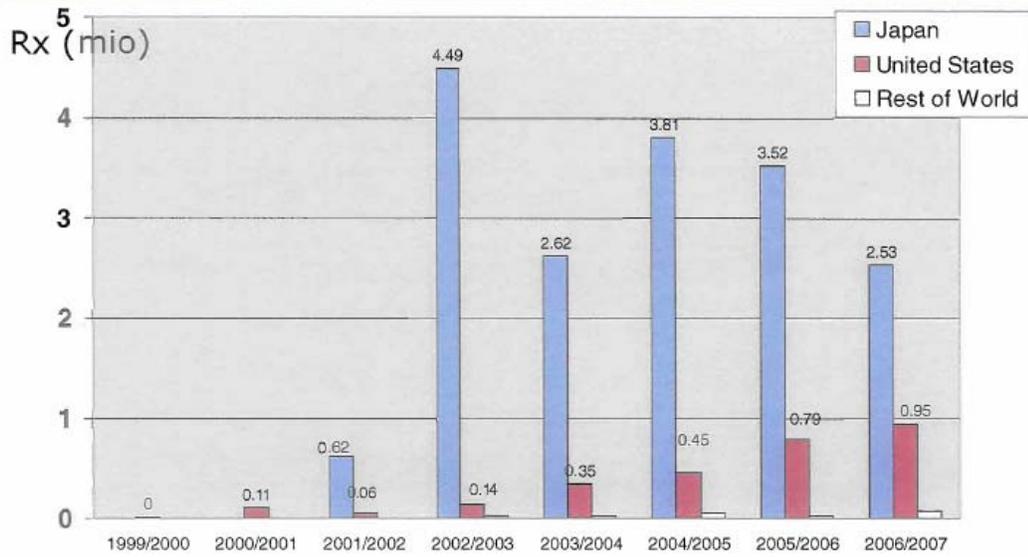
**Appendix 2. Oseltamivir Drug Use Worldwide (data courtesy of Hoffman-La Roche, Inc.)**

**Tamiflu® Prescriptions by Season and Country All Ages**



Data courtesy of Hoffmann-La Roche, Inc.  
 Japan : IMS Quarterly Rx Data until June 2007, Biannual data until June 2007  
 United States : IMS Weekly prescriptions until June 2007  
 Rest of World : IMS MIDAS Quarterly Retail data (Germany, France, Brazil, Canada) until June 2007  
 Season refers to Oct -June data only  
 Pediatric Advisory Committee November 16, 2006

Tamiflu® Prescriptions by Season and Country (≤16 yrs)



Data courtesy of Hoffmann-La Roche, Inc.  
 Japan : IMS Quarterly Rx Data until June 2007, Biannual data until June 2007  
 United States : IMS Weekly prescriptions until June 2007  
 Rest of World : IMS MIDAS Quarterly Retail data (Germany, France, Brazil, Canada) until June 2007  
 Season refers to Oct –June data only



## APPENDIX 3. DRUG USE INFORMATION:



**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: November 5, 2007  
To: Melissa Truffa, R.Ph./Safety Evaluator Team Leader  
Division of Drug Risk Evaluation  
Office of Surveillance and Epidemiology  
Thru: Laura A. Governale, Pharm.D., MBA  
Drug Utilization Data Analysis Team Leader  
Division of Surveillance, Research and Communication  
Support Office of Surveillance and Epidemiology  
From: Vicky Borders-Hemphill, Pharm.D./ Drug Use Data Analyst  
Division of Surveillance, Research and Communication  
Support Office of Surveillance and Epidemiology  
Subject: Antiviral prescriptions and Zanamivir use  
Drug Name(s): Tamiflu® (Oseltamivir); Relenza® (zanamivir);  
Symmetrel®(amantadine); Flumadine® (rimantadine)  
Application NDA 21-087 and NDA 21-246 Tamiflu® (Oseltamivir); NDA  
Type/Number: 21-036 Relenza® (zanamivir); NDA 17-118 and NDA 18-101  
Symmetrel®(amantadine); NDA 19-649 and NDA 19-650  
Flumadine® (rimantadine)  
Applicant/sponsor: Roche, GSK, and various  
OSE RCM #: 2007-1169

### 1 INTRODUCTION

The Division of Drug Risk Evaluation (DDRE) is working with the Office of Pediatric Therapeutics (OPT), Office of Pediatric and Maternal Health Staff (PMHS), and the Division of Anti-viral Products to develop an assessment of neuropsychiatric safety issues that will be discussed at the November 2007 Pediatric Advisory Committee (PAC) meeting. The differences between adverse events experienced by Japanese versus U.S. cases will be evaluated for Tamiflu and for other influenza antiviral products such as Relenza® with similar behavioral and CNS side effects. At the PAC, DDRE will be presenting safety data on all influenza antivirals and requested additional data.

On August 1, 2007, DSRCS provided an update of Tamiflu® utilization trends with a focus on the pediatric population for the two-year time period from April 1, 2005 – March 31, 2007. In addition to examining outpatient and inpatient drug utilization patterns for Tamiflu®, we examined outpatient prescription dispensing patterns for other anti-influenza products selected based on previous and ongoing post marketing surveillance.

### 2 METHODS AND MATERIAL

#### 2.1 DETERMINING SETTINGS OF CARE

We examined outpatient utilization patterns only for this review.

## 2.2 DATA SOURCES USED

We examined total dispensed prescriptions for Tamiflu<sup>®</sup> (Oseltamivir), Relenza<sup>®</sup> (zanamivir), Symmetrel<sup>®</sup> (amantadine), and Flumadine<sup>®</sup> (rimantadine) using Verispan, LLC: Vector One<sup>®</sup>: National (VONA) for five influenza seasons from July 2002-June 2007.

## 3 DATA

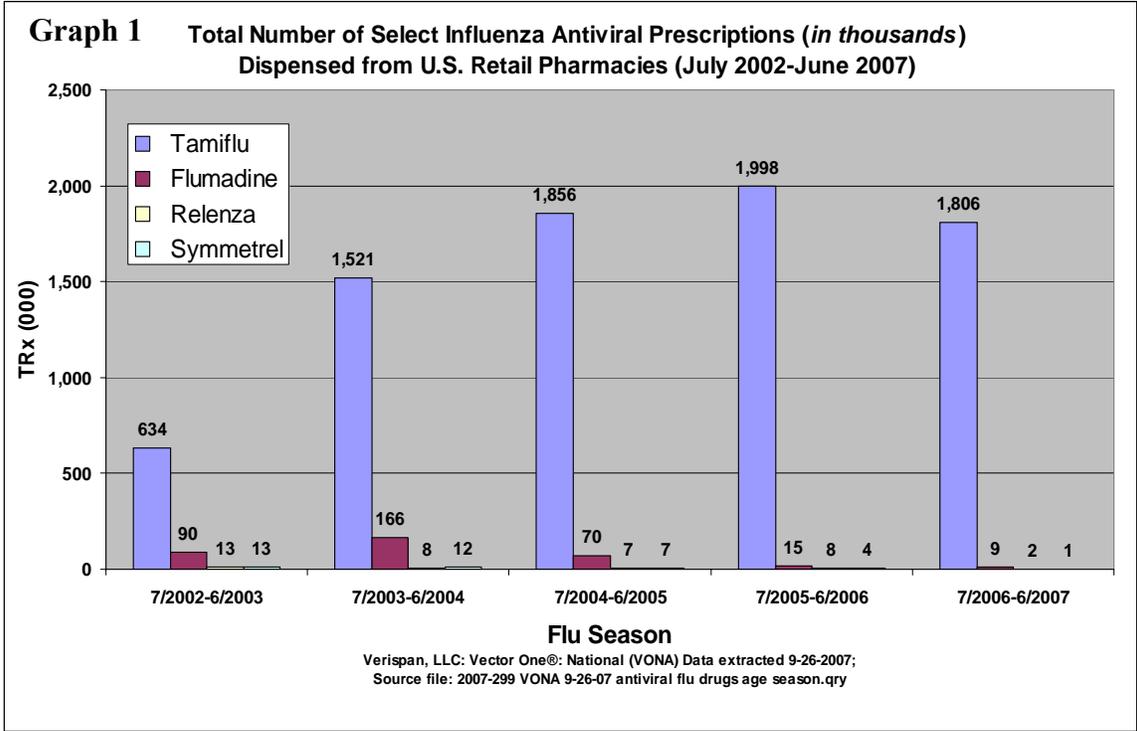
### 3.1 DISPENSED SELECT INFLUENZA ANTIVIRAL OUTPATIENT PRESCRIPTIONS

Table 1 and Graph 1 show total dispensed prescriptions for Tamiflu<sup>®</sup> (Oseltamivir), Relenza<sup>®</sup> (zanamivir), Symmetrel<sup>®</sup> (amantadine), and Flumadine<sup>®</sup> (rimantadine) for five influenza seasons from July 2002-June 2007.

- Retail dispensed prescriptions for Tamiflu<sup>®</sup> have decreased by close to 10% from the 2005/2006 influenza season to the 2006/2007 season.
- Retail dispensed prescriptions for the other select influenza antivirals have decreased substantially during the same time period; Flumadine<sup>®</sup> (decreased by 40%), Relenza<sup>®</sup> (decreased by 75%), and Symmetrel<sup>®</sup> (decreased by 75%).

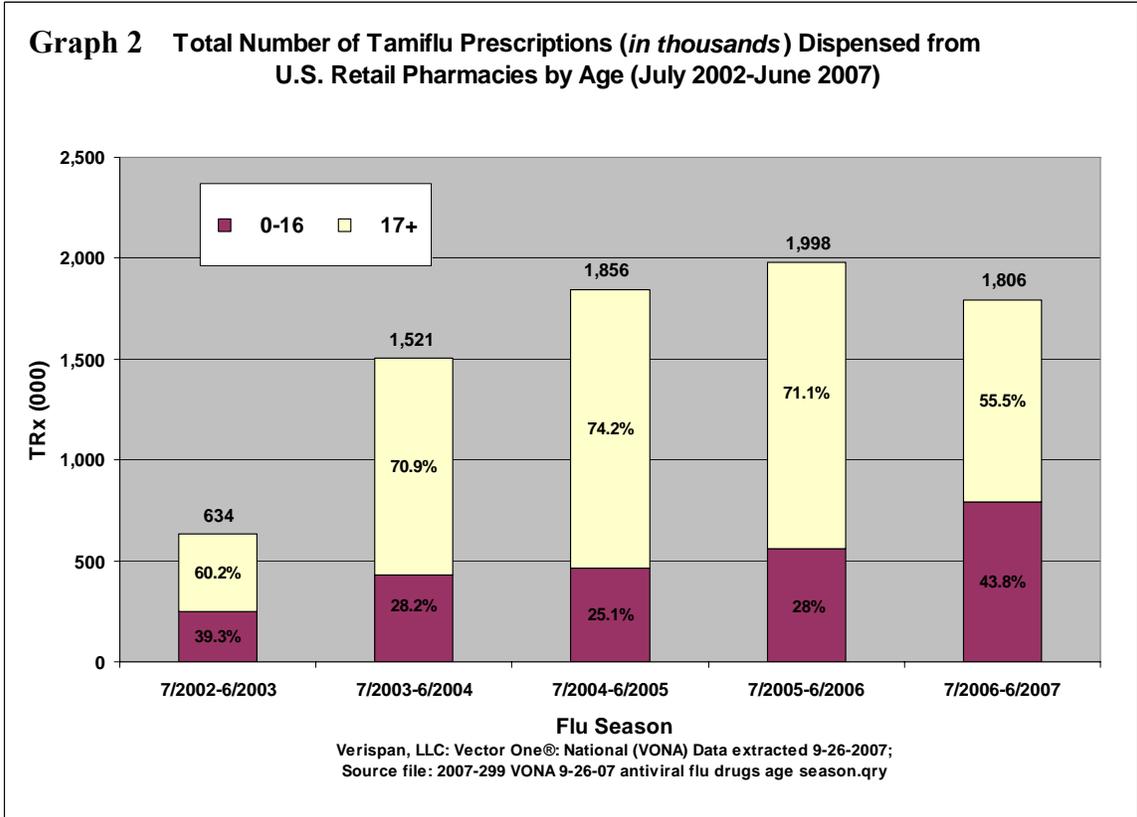
	7/2002-6/2003	7/2003-6/2004	7/2004-6/2005	7/2005-6/2006	7/2006-6/2007
<b>Tamiflu</b>	634	1,521	1,856	1,998	1,806
<b>Flumadine</b>	90	166	70	15	9
<b>Relenza</b>	13	8	7	8	2
<b>Symmetrel</b>	13	12	7	4	1

Verispan, LLC: Vector One<sup>®</sup>: National (VONA) Data extracted 9-26-2007;  
Source file: 2007-299 VONA 9-26-07 antiviral flu drugs age season.qry



### 3.2 DISPENSED TAMIFLU® OUTPATIENT PRESCRIPTIONS

Graph 2 shows that total number of Tamiflu® prescriptions dispensed from U.S. retail pharmacies by age (0-16, 17+) for five influenza seasons from July 2002-June 2007.



## 4 DISCUSSION

Tamiflu<sup>®</sup> accounts for over 98% of the select anti-influenza antiviral market. Retail dispensing of the other influenza antivirals has gradually decreased over the past five influenza seasons. The majority of Tamiflu<sup>®</sup> retail prescriptions are dispensed to patients aged 17 years and older. However, the proportion of retail prescriptions dispensed to patients aged 16 years or younger has increased over the past five influenza seasons.

## 5 CONCLUSIONS

Outpatient prescription data indicate that a greater number of Tamiflu<sup>®</sup> retail prescriptions are dispensed per influenza season when compared to the other select influenza antivirals. A substantial proportion of retail Tamiflu<sup>®</sup> prescriptions are dispensed for pediatric patients aged 16 years or less.

## APPENDIX

### *Verispan, LLC: Vector One<sup>®</sup>: 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<sup>®</sup> 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<sup>®</sup> receives over 1.5 billion prescription claims per year, representing over 100 million unique patients. Since 2002 Vector One<sup>®</sup> 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.

**APPENDIX 4. List of Excluded Cases – Oseltamivir**

<b>Reason for Exclusion</b>	<b>AERS Case Numbers</b>
Duplicate Report	3648450, 3835744, 4137701, 4137702, 4137703, 5770414, 6279509, 6286105, 6305068, 6319960
Confounded Reports	3428237, 3428241, 3457089, 3765180, 5681976, 5751256, 5754754, 5765029, 5824475, 5922062, 5978490, 5987000, 5998635, 6093358, 6253251, 6313401, 6328952
Event began before oseltamivir use or more than 3 days after last dose of oseltamivir	3539234, 3589623, 3609833, 3616232, 3627835, 3914237, 4132562, 5767199, 5777227, 6015212, 6100615, 6142972, 6239367, 6257224, 6298505, 6306649
Not neuropsychiatric event	3417684, 3436407, 3436413, 3454158, 3480122, 3616642, 3624963, 3639597, 3654281, 3661275, 3719470, 3759509, 3759526, 3761686, 3770169, 3889811, 3898709, 3901238, 3925563, 3932266, 3934666, 3944787, 3956715, 4009400, 4010817, 4100296, 4104814, 4105676, 4108055, 4115199, 4120794, 4137103, 4183222, 5758389, 5758401, 5765053, 5767161, 5770415, 5776474, 5781667, 5813141, 5815600, 5826323, 5967674, 5977474, 5986050, 5988808, 5992878, 5997691, 5998637, 6018381, 6021022, 6066687, 6090500, 6182012, 6184569, 6207132, 6229128, 6258146, 6264671, 6267482, 6280740, 6280751, 6287895, 6293019, 6316488
Received after 5/31/07	6324344, 6324362, 6324371, 6324574, 6328664, 6329317, 6329318, 6334275, 6336506, 6338563
Miscellaneous <ul style="list-style-type: none"> <li>• accidental injury</li> <li>• overdose, pt received 20x the dose</li> <li>• unclear time course for events &amp; oseltamivir use</li> <li>• Unable to evaluate further. Information from a meeting presentation stating that 12 pediatric patients got encephalopathy</li> </ul>	<ul style="list-style-type: none"> <li>• 3616751</li> <li>• 6303884</li> <li>• 6239374</li> <li>• 6163736</li> </ul>
Exclusions from separate search for visual events (may be duplicates to those appearing in the categories listed above)	
Visual event	3436320, 3445071, 3448500, 3450895, 3479729, 3480202, 3662016, 3774826, 3781722, 3807482, 3956715, 3958407, 4070410, 4121669, 4137103, 5745852, 5749666, 5764668, 6062062, 6068604, 6069443, 6090500, 6144479, 6247618, 6253247, 6263436, 6279579, 6281102, 6282043

**APPENDIX 5. List of Excluded Cases – Zanamivir**

**AERS Case Numbers for Excluded Zanamivir Cases (n=45):**

6320431, 6277300, 6272033, 3379949, 3403327, 3403364, 3404780, 3415085, 3416005, 3419839, 3424634, 3427225, 3427227, 3427865, 3437261, 3442176, 3442708, 3504909, 3504733, 3472836, 3504929, 3505897, 3505928, 3505942, 3534613, 3534665, 3534773, 3571730, 3572591, 3593988, 3599956, 3605107, 3609388, 3614821, 3617392, 3631176, 3674711, 3774026, 5963581, 5986763, 6005987, 6240732, 6075767, 6246246, and 6256359

## **APPENDIX 6. List of Excluded Cases – Amantadine**

A total of 26 amantadine cases were excluded from the review for the following reasons:

- Six patients [AERS cases # 4423061 (11M), 4477510 (17F), 3126563 (21M), 4423029 (21M), 4423031 (21M), 4423033 (21M)] with a history of seizure disorder, mental retardation and other medical conditions experienced exacerbations of convulsions and an 18-year-old male patient [AERS Case # 4642263] with history of schizophrenia and drug abuse was also receiving concomitant anti-psychotic medications stated that Symmetrel gave him the same “high”
- Three Roche Tamiflu reports [AERS cases # 4165603 (17M) Japan, 6215173 (17M) Taiwan, and 5789944 (3F) Japan] were excluded because both Tamiflu and amantadine were administered concomitantly; these cases are included in the Tamiflu section of this review
- An 18 month-old female patient [AERS cases # 4517020] experienced prolonged seizure associated with temperature elevation of 105<sup>0</sup>F
- The last two patients [AERS cases # 5091638 (11M), and 4570367 (16M)] were exclude because they had vision abnormalities that did not involved neuropsychiatric events
- Two patients [AERS cases # 6348673 (10F), 6348674 (11M)] with rabies were treated using a therapy (including amantadine) similar to a patient who survived in Wisconsin; both treatments were unsuccessful.
- Three patients experienced overdose; a 20-year-old male patient [AERS case # 5071107] who intentionally ingested seven medications including amantadine, a 10-year-old child [AERS case # 4209673] was mistakenly dispensed Symmetrel 1.9 Gm/day instead of Tegretol for epilepsy, and a 16-year-old female patient [AERS case # 5079205] exhibited confusion; she had mistakenly taking amantadine 100mg QID x 5 days instead of BID x 5 days. Her toxicological screen showed traces of amphetamine and tranquilizers.
- A 13-year-old male patient [AERS case # 6062948] with autism had been well controlled with Brand “Symmetrel” experienced flushing, agitation and increased stuttering when his medication was switched to generic amantadine.
- Four patients [AERS cases # 4063369 (9M), 5418106 (11F), 5165315 (12F), 3163407 (15F), and 4784217 (21M)] experienced hallucinations, and delusions with history of schizophrenia, self- mutilation, bipolar disorder and they were also taking concomitant anti-psychotic medications.
- AERS case # 3037329 (8M) is a litigation case due to patient had heart arrest and in coma, AERS case # 4087149 (18M) experienced convulsion while taking 24 other concomitant medications, and AERS case # 6159870 (21M) had aggravated post traumatic organic brain syndrome and Stevens Johnson syndrome.