

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**ODS PID#:** D060309

**DATE:** September 20, 2006

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**SUBJECT:** Post-Marketing Adverse Event Reports Review of central nervous system/psychiatric disorders associated with the use of Tamiflu®.  
Drug: Oseltamivir phosphate  
NDAs: 21-087 (Tamiflu® Capsules), 21-246 (Tamiflu® Oral Suspension), Roche

**\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\***

**1. EXECUTIVE SUMMARY**

The purpose of this consult is to reevaluate the occurrence of cases of neuropsychiatric adverse events reported from the postmarketing experience with Tamiflu® (oseltamivir) for either treatment or prophylaxis of influenza. During the last 10 months since the last review of neuropsychiatric adverse events dated December 16, 2005, there are increasing numbers of these events being reported. For this update, which covers the time period from 08-29-2005 through 07-06-2006 there were 129 reports of neuropsychiatric adverse events associated with the use of

Tamiflu® (oseltamivir phosphate) compared to 126 neuropsychiatric adverse event reports reviewed in the previous consult which covered the time period from the approval date in 1999 to 08-29-2005.

All 129 unduplicated reports were manually reviewed, and 26 reports were excluded from further discussion (see Appendix I). The remaining **103** neuropsychiatric adverse event reports were reviewed for this consult. Among these 103 cases, approximately 67% (68/101) are pediatric patients (0 – <17 years), 95% are foreign (with 95/103 reports from Japan). The use of oseltamivir in these reports is predominantly for the treatment of influenza (100/103) and there are three fatalities.

The patients in the three fatal cases were healthy individuals except for having influenza at the time they received oseltamivir. One patient was a 14-year-old boy who apparently fell to his death after climbing on his condominium balcony railing. Another two adult males also fell to their deaths, and one of these two left a suicide note. These three patients reportedly had not exhibited any psychological or neurologically abnormalities before they received oseltamivir therapy. There were additional reports of patients who had jumped or fallen, but survived their injuries.

As was discussed in the December 2005 review there are multiple challenges to adequately assessing a clear relationship between the use of oseltamivir and onset of these neuropsychiatric events. First, the majority of the 103 reports are foreign (95%) 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 these foreign reports because they are subjective to the choice of words from different translators. Third, the domestic reports often do not provide adequate narrative information to assess a clear relationship. Finally, 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 better characterize these 103 reports for further assessment, they are thus grouped into the following **eight** major categories according to their primary adverse event described in the narratives from each case: Category 1 – Delirium with Prominent Behavioral Disturbances (n = 60), Category 2 – Suicidal events (n = 6), Category 3 – Panic Attack (n = 3), Category 4 – Delusions (n = 3), Category 5 – Convulsions (n = 12), Category 6 – Depressed Level of Consciousness (n = 6), Category 7 – Loss of Consciousness (n = 4), and Category 8 – Miscellaneous (n = 9). For cases involving events from more than one category, a judgment was made regarding the category which best described the report.

There are a number of characteristics from this case series which deserve highlighting. First, these neuropsychiatric cases appear to be temporally related to the use of oseltamivir. In the majority of the cases, the time of onset of neuropsychiatric symptoms from the administration of oseltamivir dose was within one day (1 to 2 doses). There was only one case that reported the development of symptoms after 5 days of oseltamivir therapy. Of those cases that reported time to development of symptoms after dosing (n = 58), 12 cases or 21% reported the development of

symptoms within half an hour of receiving oseltamivir. Secondly, many of the cases reported that the physician felt that this was drug-effect (see Section 6.3 for notable summaries). Some of the reasons given by reporting physicians included rapid positive de-challenge with negative sequelae and/or lack of positive neuro-imaging findings, as well as the rapid temporal relationship between starting oseltamivir and the onset of adverse symptoms. In examining the case series as a whole, for cases which reported positive de-challenge (n = 65), there was a rapid and full recovery from the neuron-psychiatric adverse event once oseltamivir was discontinued. Further, 25 cases reported that confirmed brain CT scan/EEG/MRI revealed no abnormalities. Finally, the characteristics of the neuropsychiatric adverse events from the first and second categories (Delirium – with Prominent Behavioral Disturbances and Suicide Events: see section 5.3) are peculiar, i.e. not typical of influenza-illness reported encephalitis/delirium symptoms. We were not able to find specific cases reported in the literature which describe influenza patients “jumping or falling out of windows” to their demise. Suicide attempts/completed suicide are also quite atypical of influenza-induced delirium.

At the present time, we still cannot fully explain the association of “abnormal behavior” observed in these reports to the use of oseltamivir. It is still unclear whether these neuropsychiatric events are drug-related only, disease manifestation alone, or a combination of drug-disease expression. Further, the cases from this second year of review continue to be reported predominantly (92%) from Japan, which continues to suggest a specific genetic/population overlay to this set of adverse experiences vs. simply large exposure of Tamiflu® in Japan or both. Our recommendation in the last review dated December 16, 2005 was to continue close monitoring of these abnormal neuropsychiatric events. Given 1) the number of additional neuropsychiatric adverse events that have been reported to AERS during the last year, 2) the fact that numerous reporting physicians commented in these reports that their patient’s “abnormal behavior” was associated to oseltamivir induced adverse events (section 6.3), and 3) the peculiar characteristics of these adverse events which are different from the usual influenza-related set of central nervous system symptoms, we cannot rule out the possible contribution of oseltamivir to the adverse consequence 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 an adequate postmarketing data suggesting an association between the use of oseltamivir and the development of neuropsychiatric events. We are concerned that when/if the use of this drug increases in the U.S. to be in the realm of the current Japanese use of this drug, there may be increasing cases of adverse consequence in the U.S. as well. Therefore, it would be prudent to update the U.S. labeling to be similar in scope with the current Japanese labeling regarding neuropsychiatric adverse events. In particular, we want to alert the clinician/patient/patient’s guardian to closely monitor the patient in order to abort any attempt at unsafe behavior (i.e. suicide attempts).

- We propose the following recommended language for addition in the section of the current oseltamivir label:

[REDACTED]

[REDACTED]

- We also ask that DAVP query Roche in regards to the Japanese oseltamivir usage data for the time period from 08-29-2005 through 07-06-2006. Please forward this information to DDRE/OSE once received by DAVP.
- We will continue to monitor postmarketing reports of these adverse events. We also note that the sponsor has been asked to provide additional information regarding the publication by Okumura et al., which has the potential to be very informative.

## **2. REASON FOR REQUEST/REVIEW**

After the 2005-2006 influenza season DAVP requested a reevaluation of the occurrence of cases of CNS/neuropsychiatric adverse events reported from the postmarketing experience with Tamiflu® (oseltamivir) for either treatment or prophylaxis of influenza. This review includes events from the 2005 – 2006 influenza season and events received since the last review dated December 16, 2005.

This review evaluates the reports in all ages from August 29, 2005 through July 06, 2006.

### **3. RELEVANT LABELING FOR NEUROPSYCHIATRIC ADVERSE EVENTS**

#### **3.1 U.S. Label for Tamiflu®**

The current U.S. Tamiflu® (oseltamivir phosphate) labeling as of December 2005 contains the following terms related to neuropsychiatric adverse events under ADVERSE REACTIONS section; Observed During Clinical Practice for Treatment section; Neurologic: Seizure and confusion.

#### **3.2 Japanese Label for Tamiflu®**

The current Japanese Tamiflu® (oseltamivir phosphate) labeling as of October 2005 contains the following paragraph related to neuropsychiatric adverse events under PRECAUTIONS section; Adverse Reactions section:

##### **PRECAUTIONS**

##### **3. Adverse Reactions**

7) Psychoneurological symptoms (frequency unknown): Psychoneurological symptoms (e.g. disturbances in consciousness, abnormal behaviour, delirium, hallucination, delusion, convulsions) may occur. If any abnormality is observed, the administration should be discontinued. Patients should be carefully monitored and appropriate therapeutic measures should be taken according to individual symptoms.

### **4. METHODOLOGY**

#### **4.1 AERS Search**

**Search Type:** ☒ AERS    ☒ Literature    ☐ Other

**Search Dates:** 08-29-2005 to 07-06-2006

**Search Criteria:**

**Drug Name:** Tamiflu® (oseltamivir phosphate)

**MedDRA Terms:**

#### **NEUROPSYCHIATRIC**

- a. HLT Suicidal and Self-injurious Behaviour including the following 7 PT: completed suicide, intentional self-injury, self injurious behaviour, self mutilation, self-injurious ideation, suicidal behaviour, suicidal ideation, suicidal ideation, suicide attempt.
- b. 30 PT: abnormal behaviour, abnormal dreams, agitation, anxiety, cognitive disorder, confusional state, convulsion, delirium, delusion, delusional perception, depressed level of consciousness, disturbance in attention, encephalitis, encephalopathy, excitability, fear,

hallucination, hallucination auditory, hallucination visual, hallucination mixed, illusion, loss of consciousness, mania, mental impairment, nervousness, panic attack, panic reaction, restlessness, schizophrenia, thinking abnormal.

## **4.2 Case Definitions**

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 (95%) 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, the domestic reports often do not provide adequate narrative information to assess a clear relationship. Last, 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 reports, they are grouped into **eight** major categories according to their primary adverse event described in the narratives from each case.

Category 1 – Delirium with Prominent Behavioral Disturbances

Category 2 – Suicidal events

Category 3 – Panic Attack

Category 4 – Delusions

Category 5 – Convulsions

Category 6 – Depressed Level of Consciousness

Category 7 – Loss of Consciousness

Category 8 – Miscellaneous

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

In addition, the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV)<sup>1</sup> describes similar clinical characteristics of the abnormal behaviors that were reported in the 103 cases associated with the use of oseltamivir. They were useful in establishing the eight 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.

“Diagnostic Features (p.124)

- 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,

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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

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.

#### **4.3 Drug Use Data**

Oseltamivir was approved in the U.S. in October 1999. Drug utilization data for oseltamivir from 2000 through June 2006 were measured by the Verispan, LLC: database Vector One®: National (VONA). This data resource is an audit of prescriptions dispensed by retail pharmacies which can generate national estimates of total prescriptions dispensed. Vector One® includes data on prescriptions for an estimated >160 million unique patients, but does not include mail order prescriptions.

### **5. RESULTS**

#### **5.1 U.S. Drug Use Data**

The following table shows the total number of oseltamivir prescriptions by year (July – June), from U.S. launch, for both the capsule and liquid dosage forms.

**Total Number of U.S. Prescriptions Dispensed by Retail Pharmacies for  
Tamiflu (oseltamivir)  
Oral capsules and suspension  
by Years, Moving Annual Total (MAT)<sup>1</sup>**

<b>MAT<sup>2</sup> Jun/2000</b>	<b>MAT Jun/2001</b>	<b>MAT Jun/2002</b>	<b>MAT Jun/2003</b>	<b>MAT Jun/2004</b>	<b>MAT Jun/2005</b>	<b>MAT Jun/2006</b>	<b>Total</b>
<b>760,000</b>	<b>813,000</b>	<b>757,000</b>	<b>634,000</b>	<b>1,521,000</b>	<b>1,856,000</b>	<b>1,998,000</b>	<b>8,339,000</b>

<sup>1</sup> Verispan Vector One®: National, data extracted 08-04-2006  
Source Files: A060284-D060309 VONA 8-4-06 tamiflu2.qry

The next table displays the number of prescriptions for recent years by age group and formulation. Note that the liquid dosage form is primarily dispensed to pediatric patients.

**Total Number of U.S. Prescriptions Dispensed by Retail Pharmacies for  
Tamiflu (oseltamivir)  
Oral capsules and suspension  
by Years, Moving Annual Total (MAT)**

	MAT/JUN/2003	MAT/JUN/2004	MAT/JUN/2005	MAT/JUN/2006
<b>TOTAL</b>	<b>634,000</b>	<b>1,521,000</b>	<b>1,856,000</b>	<b>1,998,000</b>
<b>Total CAP 75MG</b>	<b>518,000</b>	<b>1,310,000</b>	<b>1,559,000</b>	<b>1,639,000</b>
0-16	135,000	223,000	178,000	210,000
17-65	356,000	952,000	1,191,000	1,205,000
66+	25,000	123,000	180,000	211,000
UNSPEC.	2,000	11,000	10,000	14,000
<b>Total SUSP 12MG</b>	<b>117,000</b>	<b>211,000</b>	<b>297,000</b>	<b>359,000</b>
0-16	115,000	205,000	287,000	349,000
17-65	1,000	2,000	6,000	5,000
66+	0	0	1,000	1,000
UNSPEC.	1,000	3,000	3,000	4,000

Source: Verispan Vector One®: National, data extracted 08-04-2006  
Source Files: A060284-D060309 VONA 8-4-06 tamiflu age2.qry

## **5.2 Japanese Drug Use Data**

Oseltamivir is widely prescribed in Japan, resulting in greater exposure compared to the U.S..<sup>2</sup>

Age group	Number of prescriptions 2001-2005	
	U.S.	Japan
All ages	6.5 million	24.5 million
Ages 0-16	0.9 million	11.6 million

## **5.3 AERS Search Results (n = 129)**

There were 129 reports of neuropsychiatric adverse events associated with the use of Tamiflu® (oseltamivir phosphate) in AERS from 08-29-2005 to 07-06-2006. The AERS search included the same 37 PT (Section 3.3), which were also provided to Roche on August 30, 2005 for use in a requested safety analysis. All 129 unduplicated reports were manually reviewed, and 26

<sup>2</sup> November 18, 2005 Pediatric Advisory Committee Executive Summary for Tamiflu® prepared by Hoffmann-La Roche



reports with age ranging from 11-month to 88-year were excluded from further discussion for various reasons (see Appendix I).

The remaining 103 neuropsychiatric adverse event reports were reviewed for this consult.

The details of the sample events for each category are as follows.

**Categories of Neuropsychiatric Events reviewed (n = 103):**

**1. Delirium with Prominent Behavioral Disturbances – 60 (US – 1) [death = 2]**

Samples of brief descriptions:

- Patient jumped or fell out of residence's window and sustained injuries or death.
- Patient ran toward the door or toward the window wanting to get out of their residence from the upper levels of single houses or high-rise buildings. They were stopped or rescued by family members before a catastrophic consequence ensued.
- Patient ran away from home but returned safely or was found unharmed.
- Patient cried out in "fear" or displayed "fear" that led to an escape attempt.
- Patient attempted to escape but was unsuccessful.
- Patient shouted that they wanted to kill everyone around them.
- Patient shouted loudly, made loud noises, or threw things.
- Patient moved about restlessly inside the house, and said delirious words.
- Patient suddenly became excited and pounded his head against the wall.

**2. Suicidal events – 6 (US – 1) [death = 1]**

- Patients had suicidal ideation, self injurious acts. One patient had a fatal outcome.

**3. Panic Attack – 3**

**4. Delusions/Hallucinations – 3**

**5. Convulsions – 12 (US – 1)**

**6. Depressed Level of Consciousness – 6**

**7. Loss of Consciousness – 4 (US – 1)**

**8. Miscellaneous (events not captured in another category) – 9 (US – 1)**

The age range for the 101 cases of neuropsychiatric events with oseltamivir where an age was listed is 1.5 to 90 years of age with an average of 21 years and a median of 12 years. There are 69 males and 32 females. The majority of the reports are from Japan 92% (95/103) and 5% (5/103) are from the U.S.

Seventy-five patients tested positive for influenza A, 3 tested positive for influenza B, 3 had negative test results for influenza, 3 were given as prophylaxis for influenza, and 19 patients were treated for influenza with no confirmed influenza information provided in the report.

The latency, time to onset of symptoms from the initiation of oseltamivir therapy, ranged from 1 to 10 doses with an average of 2 doses and a median of 1 dose. Most adverse event developed after the 1<sup>st</sup> or the 2<sup>nd</sup> dose of oseltamivir administration, which accounts for 73% (75/103) of the reports.

The clinical characteristics of neuropsychiatric events with oseltamivir from 08-29-2005 through 07-06-2006 are summarized in Table 1 and Table 2.

<b>Table 1.—Clinical Characteristics of Neuropsychiatric Events with Oseltamivir ( 08-29-2005 through 07-06-2006)</b>		
<b>Number of Cases</b>	<b>N=103</b>	
<b>Age (n = 101)</b>	Range—1.5 to 90 years Average—21 years Median—12 years	0 – <17 years (n=68) ≥17 – 21 years (n =8) > 21 years (n=25)
<b>Gender (n = 101)</b>	Female (32), Male (69)	
<b>Source (n = 103)</b>	Japan – 95 (92%), US – 5 (5%), Germany – 2, Singapore – 1	
<b>Outcome (n = 103)</b>	Death – 3 (Japan-2, Singapore-1) Life-threatening – 11 Hospitalized – 38 Disability – 1 Other/Medically significant – 50	
<b>Positive Dechallenge</b>	65	
<b>Negative Dechallenge</b>	10	
<b>Positive Rechallenge*</b>	13	
<b>Negative Rechallenge</b>	9	
<b>Indication for Use (n = 103)</b>	1. Treatment of Influenza – 100 (Type A = 75, Type B = 3)  2. Influenza Prophylaxis – 3	
<b>Latency (time to onset of symptoms from initiation of treatment)</b>	Range – 1 dose to 10 doses Median – 1 dose (n = 54) Average – 2 doses (n = 21) After 1 <sup>st</sup> or 2 <sup>nd</sup> dose of oseltamivir – 75 (73%)	
<b>8 Categories of Neuropsychiatric Events (n = 103)</b>	1. Delirium with Prominent Behavioral Disturbances – 60 (US-1) [death = 2] 2. Suicidal events – 6 (US-1) [death = 1] 3. Panic Attack – 3 4. Delusions – 3 5. Convulsions – 12 (US-1) 6. Depressed Level of Consciousness – 6 7. Loss of Consciousness – 4 (US-1) 8. Miscellaneous – 9 (US-1)	

\*Positive Rechallenge is not used as the classical definition in this review; a 2<sup>nd</sup> dose of oseltamivir administration is considered a rechallenge.

Table 2.—Tabular Summary of Clinical Characteristics of 8 Categories of Neuropsychiatric Events with Oseltamivir (08-29-2005 through 07-06-2006)

Categories (n)	Pediatrics (n) ≥ 2 – < 6 yr	Pediatrics (n) ≥ 6 – < 12 yr	Pediatrics (n) ≥ 12 – < 17 yr	Young Adults (n) ≥ 17 – < 21 yr	Adults (n) ≥ 21 yr	Dose(s) to Onset (n)	Time from Last Dose to AE (n)	Time to Resolution (n)	Positive / Negative Dechallenge Rechallenge	Fever °C (n)	Normal EEG/ MRI/ CT scan/ Neurological Exam (n)	No incident recall (n)
1. Delirium with Prominent Behavioral Disturbance (n = 60) US – 1	7 Male Female	31 Male Female	14 Male Female	4 Male Female	4 Male Female	60 Range Average Median	40 Range Average Median	48 Range Average Median	Pos Dec = 35 Neg Dec = 6 Pos Rec = 11 Neg Dec = 7	41 35.1 – 40 38 39	16) Abnormal = 2	15 Fear = 19
2. Suicidal Events (n = 6) US – 1 Prophylaxis – 1	0	0	1 Death = 1 M = 12 F = 1 U = 1	0	5 Death = 2 M = 3 F = 2 U = 1	6 1 – 8 5 6	3 2 – 12 h 8.3 h 11h	4 1 – 7 d 3.8 d 4 d	Pos Dec = 4	2 None - 38	1	2
3. Panic Attack (n = 3)	0	0	0	0	3 F = 3	3 2 – 8 5 6	1 5 d	3 same day – 4 d	Pos Dec = 3	2 36 – 38.5	1	0
4. Delusion (n = 3)	0	0	1 M = 1	1 M = 1	1 M = 1	3 4 – 10 6 5	1 1 d	3 1 h – persist	Pos Dec = 2 Neg Dec = 1	3 37.8- 39.2	1	0
5. Convulsion (n = 12) US – 1 Prophylaxis – 1	0	1 M = 1	4 M = 3 F = 1	1 M = 1	6 M = 2 F = 2	12 1 – 8 3 2	3 0.5 – 4 h	8 same day = 5 1d = 1 2 d = 1 persist = 1	Pos Dec = 6 Neg Dec = 1 Neg Rec = 2	5 36 – 39.2 38 39	1 Abnormal = 2	0
6. Depressed Level of Consciousness (n = 6)	0	3 M = 2 F = 1	0	2 M = 1 F = 1	1 F = 1	6 1 – 6 4 3	2 0.5 – 24 h	5 same day – disability	Pos Dec = 4 Neg Dec = 1	3 None – 39.1	3	0
7. Loss of Consciousness (n = 4) US – 1 Prophylaxis – 1	0	1 F = 1	0	0	3 M = 1 F = 2	4 1 – 3 2 2	1 5 h	1 1 d	Pos Dec = 3 Neg Dec = 1	3 No - 37	1	0
8. Miscellaneous (n = 9) US – 1	0	4 M = 2 F = 1 U = 1	1 M = 1	0	4 M = 2 F = 1 U = 1	9 1 – 4	8 0.3 – 6 h 5 h 2 h	8 2 – 48 h 10 h 3 h	Pos Dec = 8 Pos Rec = 8	8 38 – 40 38 39	1	1

The following table displays the time to onset of neuropsychiatric symptoms following initiation of oseltamivir treatment, for the reports containing that information. The majority occurred within 3 hours of the first dose.

**Table 3.—Time of onset of symptoms from the administration of oseltamivir (n = 58)**

Time	0.5h	1 – 1.5h	2 – 2.5h	3 – 3.5h	4h	5h	6h	12h	24h
n (%)	12 (21)	12 (21)	8 (14)	6 (10)	8 (14)	4 (7)	3 (5)	1 (2)	3 (5)

## **6.1 Notable Cases for Treatment of Influenza**

### ***Category 1.— Delirium with Prominent Behavioral Disturbance***

**Case # 5934574, Japan:** Literature: Koide A, Impulsive Abnormal Behavior following Administration of Oseltamivir Phosphate (Tamiflu). Japanese Journal of Pediatrics; 59(2):277-280(2006.2) reported an 8-year-old male patient received oseltamivir dry syrup for influenza A (diagnosed by a quick influenza test) and other concomitant medications: dextromethorphan hydrobromide, L-carbocysteine, and acetaminophen. The patient took a nap after taking his 1<sup>st</sup> dose of oseltamivir. About an hour and a half later, the patient suddenly got up and tried to run out of the front door. His mother managed to catch him in her arms at the door. He was in a state of unrest. He could not answer to his own name or this brother's and he was growling. The physician instructed the mother to pay attention to her son so that he would not get out of the room. Gradually "abnormal behavior" became less intense, and the patient increasingly regained his memory. After he became calmer, he visited the reporting hospital. He had a temperature of 38.1°C and rapid pulse and respiration. No cyanosis or abnormality in the chest- abdominal area was noted. Reddening of the pharynx was observed. Neurological findings showed clear consciousness and no orientation disturbance. There was no abnormality present in the motor system, sensory system, cerebral nerves, or cerebellum. All medications including Tamiflu were discontinued and no "abnormal behavior" was noted. The patient had only low grade fever 2 days later, and was making a satisfactory recovery. Four days later, he went to school as usual. Given the recovery course, no psychological assessment or brain wave tests were considered necessary and hence were not performed.

The reporting physician commented that "influenza encephalitis or influenza encephalopathy was excluded from the possibility of causing "abnormal behavior" because his recovery from the event was extremely rapid. The blood-brain barrier may have been impaired by influenza, and Tamiflu, for some reason, acted as a trigger and adversely affected the brain transiently. In addition, it was also possible that an interaction between Tamiflu and other concomitant drugs also acted in similar fashion. Convulsion due to Theodur (theophyllin) could resolve before it reaches the maximum blood concentration. Similarly, the onset of "abnormal behavior" was before Tamiflu became active, and the event resolved around when Tamiflu activity was at its maximum. Based on these points, "abnormal behavior" was considered to be related to Tamiflu."

**Case #5972735, Japan:** This report describes a 13-year-old patient of unspecified gender who after receiving one dose of oseltamivir for influenza was observed running towards the window of a 9<sup>th</sup> floor condominium, screaming about being chased by “hobs,” evidently hallucinations. No injuries resulted. The patient had a history of less severe hallucinations during other febrile illnesses.

**Case #5992868, Japan:** This report described an 11-year-old boy who after two doses of oseltamivir for influenza fell from a first floor landing and sustained a skull and femur fracture. The patient had complained of headache prior to the event, raising the possibility of encephalitis, although other neurological deficits were apparently absent.

**Case #5975189 (Japan):** This case involved a 7-year-old boy who 30 minutes after a single dose of oseltamivir began screaming and ran out of his house, and was found later at a neighbor’s house. He was hospitalized, but the behavioral symptoms did not return.

### ***Category 2.—Suicidal Events***

**Case # 5929190, US:** a 40-year-old male patient received Tamiflu for influenza. He began to experience severe anxiety attacks after taking the third dose of Tamiflu. The patient reported to have had a racing heart, and was unable to sleep for more than 15 minute periods. He remained in a state of high anxiety and became suicidal after the 7<sup>th</sup> dose of Tamiflu. The patient was taken to the emergency room in a suicidal state. The patient stopped taking Tamiflu after the 7<sup>th</sup> dose, and the anxiety diminished with a week of discontinuation of the medication. The patient had not experience anxiety attacks prior to taking Tamiflu. He had no other relevant medical history other than having influenza at the time of the incident.

**Case # 5942606, Japan:** a 56-year-old male patient who took Tamiflu for influenza at night. Two hours later, the patient experienced “psychiatric symptoms;” he suddenly went into depression and wanted to commit suicide by jumping off from his room, which was on the 9<sup>th</sup> floor of a condominium. The patient managed to stop himself from committing suicide, thinking of his children and went to bed early. The next morning, his “psychiatric symptom” resolved, and he chose to stop taking Tamiflu.

The reporting physician considered that “psychiatric symptom” was probably related to Tamiflu.

### ***Category 6.—Depressed Level of Consciousness***

**Case # 5961401, Japan:** Literature: Noriko N et al, A Case of Childhood Influenza Encephalitis with Atypical MRI Findings, the 428th Kanto Regional Meeting for Japan Radiological Society (2005.12.10)13, reported a 6-year-old male patient who tested positive with influenza A and treated with oseltamivir. “On the following day, “Depressed level of consciousness” (1 to 10 on the Japan coma scale) developed. Two days after taking Tamiflu, she was admitted to the hospital. Head MRI showed symmetrical high signal on the white matters of the corpus callosum and bilateral corona radiata on T2-weighted imaging and diffusion-weighted imaging. Although there was no abnormality in the basal ganglia, which seemed to be atypical for influenza encephalitis on the MRI images, influenza encephalitis was diagnosed clinically, given

that the patient was having influenza A and impairment of consciousness. On the following day of admission, Glyceol and an anticonvulsant were administered, and Tamiflu was discontinued for the possibility that “Depressed level of consciousness” was drug-induced. On the following day of discontinuing Tamiflu, clinical symptoms started improving. On hospitalization day 8, the lesions were absent on MRI.”

Comment: There was clear evidence of influenza encephalitis in this case, but there was also concern that use of oseltamivir was contributing to the patient’s altered mental status.

## **6.2 Notable Case for Prophylaxis of Influenza**

### ***Category 1.— Delirium with Prominent Behavioral Disturbance***

**Case # 5935560, Japan:** a 14-year-old junior high school student who received Tamiflu for influenza prevention and experienced “delirium” and “suicide attempt.” The patient had cough, pharynx pain, arthralgia, and pyrexia of 38°C on 2/26/05. She received an antipyretic and her symptoms did not improve. She visited the hospital on 2/28/05, and was prescribed Clarith (clarithromycin) for adenoiditis and Tamiflu to prevent influenza as she has not received influenza vaccination and influenza was epidemic at that time.

The patient took the drugs in the evening. In the morning of 3/2/05, she experienced “hallucination” and “persecutory delusion;” she said “somebody was watching me from outside,” “a stranger in our house” and “the salad is poisoned.” She showed abnormal behavior such as opening all the windows in the house despite the cold weather and wandering around in the house restlessly. Tamiflu was discontinued. Her mother took her to a psychiatric department of a university hospital where she received an injection of “stabilizer.” “Delirium” was diagnosed.

On 3/4/05, she calmed down slightly but made remarks suggesting “suicide attempt;” she said that she wanted to die and her mother was going to kill her.” On 3/5/05, she calmed down more and returned to a normal state. The patient was noted to have weight loss of 2 Kg. Thereafter, abnormal behavior or “delirium” did not redevelop.

The reporting physician commented that “she did not have medical history of epilepsy or other mental disorders. It was highly likely that Tamiflu was related to the events because she returned to a normal state 3 days after discontinuing the drug and because neurological symptoms or high degree of fever that would cause encephalosis were not observed.”

## **6.3 Notable Reporting Physicians’ Comments**

### ***Category 1.— Delirium with Prominent Behavioral Disturbance***

1. **Case # 5956430, 7M:** “MRI, CT scan, and EEG revealed no evidence that suggested encephalitis or encephalopathy. If “abnormal behavior” had not been related to Tamiflu, there would be no other factor to which the event could be attributed.”

2. **Case #5937998, 8M:** “The symptoms and fever patterns in this case did not match the ones that are observed in fever delirium, and it was considered that “delirium” was brought by the initial administration of Tamiflu. There was no “abnormal behavior” observed when the patient’s fever was 39.1 later at 11:00 PM. The next morning at 3:00 AM, the patient’s fever was relatively low (38.6), “abnormal behavior” was observed, therefore, “delirium” was most likely a side effect of Tamiflu.”
3. **Case #5968640, 8M:** “Possible explanations regarding “abnormal behavior” were as follows: encephalopathy associated with influenza was present; he was experiencing complex partial seizures; or the event was an adverse event of Tamiflu.”
4. **Case 5950567, 9F:** “The abnormal behavior observed in the patient was considered not to be delirium observed commonly during influenza because they occurred when she had no fever. Also EEG did not find any sign of phrenitis or encephalopathy, and she had no memory of exhibiting the abnormal behaviors. She had no history of febrile delirium or nightmares, and Tamiflu was most definitely related to the event.”
5. **Case #5999158, 9F:** “After taking Tamiflu in he morning, she showed “abnormal behavior” in the evening; she walker around in the room. Tamiflu was discontinued subsequently, and no “abnormal behavior” was observed on the following day. At that time she still had fever of about 39 C hence “abnormal behavior” was attributed to Tamiflu.”

#### ***Category 5.— Convulsions***

6. **Case #6005952, 12F:** “Influenza encephalopathy is defined by the influenza encephalopathy issued in 2005 as acute “disturbance fro consciousness associated with influenza.” Blood and head image testing found not abnormality. On day 1 Tamiflu was stated, and on Day 2 the temperature decreased to 36 degrees, her average temperature, without any accompanying symptom. She was afebrile and fine and resting t home. Tamiflu was continued until day 4. In the early morning of day 5, “convulsion” and consciousness disturbed” developed. The abnormal EED findings were unlike the one describe in the guideline, and hence a diagnosis of influenza encephalopathy could not be made.”

#### ***Category 6.— Depressed Level of Consciousness***

7. **Case #5961401, 6F:** Literature report- Noriki Nagaro, A case of childhood influenza encephalitis with atypical MRI findings. The 428<sup>th</sup> Kanto Regional Meeting of Japan Radiological Society (2005.12.10)13.  
 “Depressed level of consciousness was considered to be related to Tamiflu for the following reasons; on day 4 of influenza, which was the second day of Tamiflu treatment, symptoms indicating depressed level of consciousness developed. The symptoms rapidly improved the next day and the day after that of Tamiflu discontinuation. Head MRI findings obtained during the onset of the event were atypical for influenza encephalopathy. However, the possibility of influenza encephalopathy could not be

necessarily ruled out because there were variations in patterns of the encephalopathy, and the patterns observed in the patient were similar to the one of drug induced encephalopathy due to 5-FU.” “The findings atypical for influenza encephalopathy included no abnormality in the cortex or basal ganglia were found and patterns of acute necrotizing encephalopathy, diffused brain edema, and of cortical lesion, all of which were typically seen in influenza encephalopathy, were not observed in the patient.”

8. **Case #5999161, 17M:** “Tamiflu was prescribed for influenza (although definite diagnosis was not made). On the same day as he became afebrile, “consciousness disturbed” developed. Hence “consciousness disturbed” was considered to be drug-induced rather than caused directly by influenza.”

#### ***Category 7.— Loss of Consciousness***

9. **Case # 5991008, 45F:** “Loss of consciousness” was considered to be possibly related Tamiflu in view of the facts that the fever caused by influenza had already decreased to 37°C when the event occurred, and that no other flu symptom was concurrently observed. Considering that the event occurred after the second dose, the event was presumed to have occurred when the blood concentration of Tamiflu reached a certain level. Based on the fact that “loss of consciousness” did not recur during the subsequent continuous treatment with Tamiflu, it was extrapolated that exposure to an increase in the blood concentration after the first dose may have played a key role for the onset. “Loss of consciousness” in this case, although being a temporal event, was suspected to be related to Tamiflu because it occurred while other flu symptoms had been alleviated. The factor other than Tamiflu that may have caused “loss of consciousness” was influenza.”

#### ***Category 8.— Miscellaneous***

10. **Case #6017762, 7F:** “The high grade fever or influenza was thought to have been unrelated to vertigo because the event did not redevelop even while patient was febrile.”

#### **6.4 Cases with fatal outcomes (n = 3, Japan)**

There is one fatal pediatric case, #5787263, (Category 1-Delirium with Prominent Behavioral Disturbance), which involved a 14-year-old boy diagnosed with influenza A from a quick diagnostic test. Two hours after he took one capsule of oseltamivir, he was found lying barefoot in front of his condominium building where he resided on the 9<sup>th</sup> floor. No disturbed consciousness or mental symptoms were present at the time he visited the clinic. “The police said that the patient’s 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. It was reported that this teenage boy who had taken antiviral drug oseltamivir exhibited abnormal behaviour that lead to this death. This was reportedly the first time that death has been linked to the drug. The Ministry of the Health, Labor and Welfare, stated “as a result of abnormal behaviour, it could lead to an accidental death.” The event was assessed as related to oseltamivir.”



The other two fatalities (both from Category 2 – Suicidal Events) are in adult male patients, 44 and 51 years of age, respectively.

**Case # 5996189** involves a 44-year-old male treated with oseltamivir 75 mg twice daily for influenza; 2 days later he committed suicide. The reporting physician stated that “the patient had looked healthy and did not suffer from any other known ailments. However, they were unwilling to provide further details with regards to how the patient died other than that the patient had “fallen to their death” and that an “open verdict” had been found by a coroner.”

**Case # 6008106** describes a 51-year-old man admitted to the hospital due to common cold and respiratory failure associated with old tuberculosis. After the admission, the patient did not show behavior such as self-resentment or self-rejection; he did not have depression or was not in a depressed state. Around 6 pm the patient expressed anxiety about his future health and physical condition. He was told that the anxiety symptoms were going to be examined and treated individually. He tested positive for Influenza A, and oseltamivir was administered at 7 pm only once. After oseltamivir administration, psychiatric or neurological symptoms were not observed. The next morning around 5 am, it was confirmed that the patient was alive. At 6:30 am, it was found that he was not in the bed. Around 7 am, he was found dead on the street in front of his hospital room on the 4<sup>th</sup> floor. His writing in his suicide note did not suggest the presence of any altered mental status. The reporting physician commented that “during the hospitalization, he experienced numbness of the lower limbs as a complication, and he was showing vague anxiety about his future health before Tamiflu administration. It was unknown whether oseltamivir had pharmacologically reached to the central nervous system. It was based on the fact that Tamiflu was administered to the patient that Tamiflu was suspected to have been related to “suspicion of psychiatric symptom” and “suicide.” Although Tamiflu was considered to have had little influence on “suicide” and his mental state, the possibility could not be completely ruled out.”

The patients in these three fatal cases were healthy individuals except for having influenza at the time they received oseltamivir. These patients did not exhibit any psychological or neurologically abnormalities before they received oseltamivir therapy. Therefore, these three deaths are possibly related to the use of oseltamivir.

### **6.5 Domestic Cases (n = 5)**

There were only 5 domestic cases returned in AERS search. Please see Appendix II for details.

## **7. DISCUSSION**

There were 126 neuropsychiatric adverse event reports reviewed in the December 2005 consult<sup>3</sup> with the use of oseltamivir in all ages from the approval date in 1999 to August 29, 2005. During the last 10 months (08-29-2005 to 07-06-2006) since the last consult, there are increasing numbers of neuropsychiatric events being reported; 103 such cases are reviewed for this consult.

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<sup>3</sup> ODS PID # D050502, December 16, 2005. Section 6. NEUROPSYCHIATRIC EVENTS: p. 9-15

Among these 103 cases, approximately 67% (68/101) are pediatric patients (0 – <17 years), and male patients predominate with 74% (50/68).

The patients in the three fatal cases, all three of which involved either intentional or accidental self-injury did not exhibit any psychological or neurological abnormalities before they received oseltamivir therapy. Therefore, these three deaths are possibly related to the use of oseltamivir.

Obviously at issue regarding these case reports is whether such neuropsychiatric abnormalities can occur in the course of influenza without exposure to oseltamivir. Influenza-associated encephalopathy has been increasingly recognized in Japan, primarily in children, but often has more profound neurological deficits; in one case series of 89 pediatric influenza encephalopathy patients, 88 developed unconsciousness and 68 developed seizures.<sup>4</sup> However, neuropsychiatric symptoms have been observed in the absence of frank encephalopathy. In a case series describing 84 children requiring hospitalization for influenza A (but not necessarily with influenza encephalitis), visual hallucinations were noted in 9 out of the 84 children and confusion was observed in 18 of the 84; both the hallucinations and the confusional state were more frequent among children over 5 years old.<sup>5</sup> In an article about influenza A-associated CNS dysfunction in children Huang YC et al.<sup>6</sup> described five children ages 3-6 years with visual hallucinations and inappropriate behavior; the time to onset was within 3 days of influenza symptoms. Delorme L and Middleton PJ<sup>7</sup> described a 5-year-old boy with influenza A and neurobehavioral symptoms without isolation of the virus from the CNS, suggesting that such symptoms can occur without actual CNS viral infection. A very recent report by Okumura et al.<sup>8</sup> described a retrospective survey for delirious behavior among children treated with oseltamivir in their system of hospitals. They report that 4/6121 children treated with oseltamivir developed delirious behavior, and that 5 children not treated with oseltamivir (out of an unspecified total) displayed delirious behavior. (Unfortunately this publication is only a brief summary. It would be very useful to obtain more clinical information regarding those 9 cases, and to find out how many untreated children there were in their survey, so that the incidence of delirious behavior with or without oseltamivir might be compared.)

On balance, it appears that influenza illness can result in neuropsychiatric disorders in the absence of exposure to oseltamivir, although the characteristics of the oseltamivir + influenza cases are peculiar and not typical of influenza-illness only neuropsychiatric symptoms in regards to the suicide-attempt type of behavior cases. What is not known is to what extent oseltamivir treatment contributed to the cases of neuropsychiatric symptoms described herein. Although reports of neuropsychiatric symptoms with prophylactic use in a healthy patient would be more persuasive for a direct causal relationship to oseltamivir; we were unable to identify such a case at this time.

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<sup>4</sup> Togashi T, Matsuzono Y, Narita M, Morishima T. Influenza-associated acute encephalopathy in Japanese children in 1994-2002. *Virus Research* 103(2004) 75-78.

<sup>5</sup> Wang YH, Huang YC, Chang LY, Kao HT, Lin PY, Huang CG, Lin TY. Clinical characteristics of children with influenza A virus infection requiring hospitalization. *J Microbiol Immunol Infect* 2003;36:111-6.

<sup>6</sup> Huang YC, Lin TY, Wu SL, and Tsao KC. Influenza A-associated central nervous system dysfunction in children presenting as transient visual hallucination. *Pediatr Infect Dis J* 2003;22:366-8.

<sup>7</sup> Delorme L, Middleton PJ. Influenza A virus associated with acute encephalopathy. *Am J Dis Child* 1979;133:822-4.

<sup>8</sup> Okumura A, Kubota T, Kato T. Oseltamivir and delirious behavior in children with influenza (letter). *Ped Inf Dis J* 2006 Jun;25(6):572.

There are a number of characteristics from this case series which deserve highlighting. First, these neuropsychiatric cases appear to be temporally related to the use of oseltamivir. In the majority of the cases, the time of onset of neuropsychiatric symptoms from the administration of oseltamivir dose was within one day (1 to 2 doses). There was only one case that reported the development of symptoms after 5 days of oseltamivir therapy. Of those cases that reported time to development of symptoms after dosing (n = 58), 12 cases or 21% reported the development of symptoms within half an hour of receiving oseltamivir. Secondly, many of the cases reported that the physician felt that this was drug-effect (see Section 6.3 for notable summaries). Some of the reasons given by reporting physicians included rapid positive de-challenge with negative sequelae and/or lack of positive neuro-imaging findings, as well as the rapid temporal relationship between starting oseltamivir and the onset of adverse symptoms. In examining the case series as a whole, for cases which reported positive de-challenge (n = 65), there was a rapid and full recovery from the neuron-psychiatric adverse event once oseltamivir was discontinued. Further, 25 cases reported that confirmed brain CT scan/EEG/MRI revealed no abnormalities. Finally, the characteristics of the neuropsychiatric adverse events from the first and second categories (Delirium – with Prominent Behavioral Disturbances and Suicide Events: see section 5.3) are peculiar, i.e., not typical of influenza-illness reported encephalitis/delirium symptoms. We were not able to find specific cases reported in the literature which describe influenza patients “jumping or falling out of windows” to their demise. Suicide attempts/completed suicide are also quite atypical of influenza-induced delirium.

We were unable to find clear data on whether oseltamivir or its metabolite crosses the blood-brain barrier. Obviously, central nervous system effects from the drug would appear more plausible if the compound crosses the blood-brain barrier. Straumanis, JP et al.<sup>9</sup> described treatment of a case of influenza B encephalitis with oseltamivir. The patient was a 10-year-old boy who became comatose and was found to have influenza B RNA in his CSF. He received oseltamivir and the viral RNA was no longer detected in his CSF; the authors speculate that the drug may have crossed the blood brain barrier.

With respect to the Japanese origin of the cases, one might speculate that these neuropsychiatric disorders are somehow related to genetic characteristics found more commonly in the Japanese population than in the US. However, given the much greater use of the drug in Japan than in the US, and possible differences in postmarketing surveillance practices between the two countries, the relative scarcity of US reports should not be viewed as meaningful evidence in favor of such a hypothesis.

## 8. CONCLUSIONS/LABELING RECOMMENDATIONS

At the present time, we still cannot fully explain the association of “abnormal behavior” observed in these reports to the use of oseltamivir. It is still unclear whether these neuropsychiatric events are drug-related only, disease manifestation alone, or a combination of drug-disease expression. Further, the cases from this second year of review continue to be reported predominantly (92%) from Japan, which continues to suggest a specific

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<sup>9</sup> Straumanis JP, Tapia MD, King JC. Influenza B infection associated with encephalitis: treatment with oseltamivir. *Pediatr Infect Dis J* 2002;21:173-5.

genetic/population overlay to this set of adverse experiences vs. simply large exposure of Tamiflu® in Japan or both. Our recommendation in the last review dated December 16, 2005 was to continue close monitoring of these abnormal neuropsychiatric events. Given 1) the number of additional neuropsychiatric adverse events that have been reported to AERS during the last year, 2) the fact that numerous reporting physicians commented in these reports that their patient's "abnormal behavior" was associated to oseltamivir induced adverse events (section 6.3), and 3) the peculiar characteristics of these adverse events which are different from the usual influenza-related set of central nervous system symptoms, we cannot rule out the possible contribution of oseltamivir to the adverse consequence 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 an adequate postmarketing data suggesting an association between the use of oseltamivir and the development of neuropsychiatric events. We are concerned that when/if the use of this drug increases in the U.S. to be in the realm of the current Japanese use of this drug, there may be increasing cases of adverse consequence in the U.S. as well. Therefore, it would be prudent to update the U.S. labeling to be similar in scope with the current Japanese labeling regarding neuropsychiatric adverse events. In particular, we want to alert the clinician/patient/patient's guardian to closely monitor the patient in order to abort any attempt at unsafe behavior (i.e. suicide attempts).

We propose the following recommended language for addition in the PRECAUTIONS section of the current oseltamivir label. We have included proposed language recommending discontinuation of oseltamivir at the onset of neuropsychiatric adverse events, as is currently stated in the Japanese prescribing information. However, it should be recognized that if these events are due entirely to the underlying influenza infection, and if oseltamivir may have therapeutic benefit for influenza-associated encephalitis as suggested by the case report of Straumanis et al., this would actually be an incorrect strategy.

Thus, we recommend for your consideration the following language for the Tamiflu® label:

### **PRECAUTIONS**

***Neuropsychiatric Events:** There have been postmarketing reports, predominantly from Japan, of neuropsychiatric events (abnormal behavior, delirium, hallucinations, delusions, aggression, suicidal ideation, and other mental status changes) with the use of oseltamivir for the treatment of influenza, primarily among pediatric and adolescent patients, but also in adults. In extreme cases, patients have engaged in dangerous behaviors, such as running away or jumping from heights, resulting in injury or death. The relative contribution of exposure to the drug versus the influenza-illness itself to the development of these neuropsychiatric events is not known.*

*Patients, especially pediatric and adolescent patients, should be monitored closely for such abnormal behavior. This close monitoring is particularly important after first starting treatment with oseltamivir because the median time to onset of symptoms in postmarketing reports was 1-2 doses. If Patients develop abnormal behaviors, their healthcare provider should be contacted immediately to determine appropriate treatment and whether their Tamiflu® (oseltamivir) therapy should be discontinued.*

*This information should also be included in **Information for Patients under PRECAUTIONS** and the **Patient Information sheet**.*

We also ask that DAVP query Roche in regards to the Japanese oseltamivir usage data for the time period from 08-29-2005 through 07-06-2006. Please forward this information to DDRE/OSE once received by DAVP. In addition, we note that the sponsor has been asked to provide additional information regarding the publication by Okumura et al., which has the potential to be very informative. We will continue to closely monitor postmarketing reports of these adverse events through this coming influenza season.

## Appendix I

Twenty-six (26) reports are excluded for the following reasons:

- Reports are coded with abnormal behavior, delirium, hallucination, encephalitis, but, no descriptions of the events were provided to enable assessment. (n = 8)
- Patients have history of convulsions/uncontrollable convulsions, and are also currently taking anticonvulsants. (n = 4)
- Medication errors: an 88-year-old woman experienced depressed level of consciousness due to pulmonary disorder that could have developed by taking eight capsules of Tamiflu (600mg) during the night before; a 15-year-old girl mistakenly took three capsules of Tamiflu and developed depressed level of consciousness; an 8-year-old boy developed depressed level of consciousness as he was given Seroquel (quetiapine) for schizophrenia instead of the prescribed oseltamivir; a 7-year-old boy from the U.S. received Tamiflu 5 times a day experienced hallucination and vomiting. (n = 4)
- Patients had developed concurrent severe medical events during oseltamivir therapy i.e., encephalopathy due to cardio-respiratory arrest, mental impairment from high fever of 101 to 103<sup>0</sup>F. (n = 2)
- A 20-year-old male patient with family history of manic-depression disorder experienced mania. (n = 1)
- A 16-year-old female patient with history of depression and mild manic state has been taking anti-psychotics, anti-anxiety drugs, and hypnotics. She experienced psychosis. (n = 1)
- A 70-year-old female patient with history of diabetes and fell due to hypoglycemia. She then was admitted to the hospital for schizophrenia without explanation. (n = 1)
- A 54-year-old male patient with liver cirrhosis experienced loss of consciousness that could be due to hepatic coma or hyperammonemia. (n = 1)
- A 79-year-old female patient experienced loss of consciousness after she fell down on the way to the lavatory; Tamiflu was a concomitant drug during her therapy with zolpidem that required her to stay in bed for 7 – 8 hours after administration of the drug due to loss of coordination. (n = 1)
- A 66-year-old female patient suddenly fell unconscious in the bathroom with blood all over the toilet 2.5 hours after receiving Tamiflu. She had lower abdominal pain, melena and vomit. (n = 1)
- A 3-year-old girl received an injection of Japanese encephalitis vaccine one day before Tamiflu therapy started, she experienced loss of consciousness that could have been caused by Zaditen (ketotifen fumarate), her chronic asthma maintenance medication that is currently labeled for transient loss of consciousness. (n = 1)
- An 11-month-old boy was already diagnosed with influenza encephalitis and brain edema before receiving Tamiflu. (n = 1)

Appendix II.— Summary of 5 Reported US Cases of Neuropsychiatric Events Associated with Oseltamivir from 08-29-2005 to 07-06-2006								
#	Case # / (MCN)	Age (yr), Sex	Past Medical history	Categories/Reported event(s)	Event Outcome	Oseltamivir Dose, Frequency & Route	Time to Event Onset	Con. Meds
1	5929190 (Direct)	40 Male	None	1. Delirium with Prominent Behavioral Disturbance SUICIDAL IDEATION, ANXIETY, HEART RATE INCREASED, INSOMNIA	Pt stopped taking Tamiflu after the 7 <sup>th</sup> dose, and the anxiety diminished within a week.	2 QD PO Dose: unknown	3 doses	None
Pt. without previous history of similar episodes experienced anxiety attacks, "racing heart," insomnia, and suicidal ideation requiring emergency room visit, beginning after third dose. Resolved within one week of discontinuing oseltamivir.								
2	6022335 (US-ROCHE-442649)	16 Female	None	2. Suicidal Events ABNORMAL BEHAVIOUR, HALLUCINATION, PSYCHOTIC DISORDER, SWELLING FACE, HALLUCINATIONS, MIXED, INSOMNIA	Unknown	One teaspoonful BID PO	7 doses	None
Pt. without previous history of psychosis had a febrile illness and was treated with oseltamivir. After 3 ½ days of treatment developed abnormal behavior, insomnia, and subsequently hallucinations and psychosis requiring inpatient psychiatric treatment. Treating physician did not attribute this episode to oseltamivir.								
3	5978667 (396138)	Unknown Male	None	5. Convulsion CONVULSION	Resolved on the same day	75 mg BID PO	2 doses	None
Pt. hospitalized for unspecified reason had episode deemed a seizure by nurse but not considered a seizure by the patient's physician. EEG after the event was normal. Indication for oseltamivir was viral symptoms.								
4	6006998 (US-ROCHE-439763)	10 Female	Asthma, ovarian cyst, irregular menses	8. Miscellaneous Events LOSS OF CONSCIOUSNESS, DRUG INTERACTION, OEDEMA PERIPHERAL, ORTHOSTATIC HYPOTENSION, RASH, DIZZINESS POSTURAL	Resolved	75 mg QD PO	3 doses	Drosperone (Yasmin)
Pt. experienced syncope, rash, swollen fingers, and orthostatic hypotension while receiving oseltamivir for <b>prophylaxis</b> and concomitant drosperone for ovarian cyst/irregular menses, although patient was on placebo for drosperone at the time of event.								
5	5729708 US-ROCHE-393408	Unknown Male	None	8. Miscellaneous Events HALLUCINATION	Resolved	75 mg BID PO	1 day	None
Pt. receiving oseltamivir for influenza experienced hallucinations (not otherwise described) which resolved after oseltamivir was discontinued.								