Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarket Adverse Event Review

Date:	24 April 2012
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Product Name(s):	Tamiflu (oseltamivir)
Pediatric Exclusivity Approval Date:	February 22, 2010
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Applicant/Sponsor:	Roche
OSE RCM #:	2012-328

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EXECUTIVE SUMMARY

The Division of Pharmacovigilance (DPV) was asked to summarize post-marketing reports of adverse events associated with the use of oseltamivir (Tamiflu) in pediatric patients (0-16 years of age) to update the May 2012 Pediatric Advisory Committee. A comprehensive review of the adverse event profile of oseltamivir in pediatric patients that included a focus on neuropsychiatric adverse events was last conducted in 2007 in preparation for the Pediatric Advisory Committee held that year.

The main focus of this review is deaths and serious unlabeled adverse events in all pediatric patients (0 to 16 years) with an additional assessment of deaths and serious unlabeled events in infants ≤ 12 months of age. We also performed a broad assessment of neuropsychiatric adverse events in the aforementioned populations. The Adverse Event Reporting System (AERS) database was searched from June 1, 2007, through December 31, 2011, to provide an update since the 2007 pediatric oseltamivir review.

The AERS search retrieved 902 serious AE reports (crude count) across all pediatric age groups, including 112 deaths (unique cases). Pediatric AE reports (serious and non-serious) represented approximately 28% of the total oseltamivir reports in AERS (1139/4127) (crude count), pediatric deaths (n=112) represented 3% of all oseltamivir reports. The 42 cases (unique) of serious infants (≤ 12 months) AEs represented approximately 1% percent of all oseltamivir reports.

Of the 112 pediatric deaths reviewed, most deaths appeared to be related to complications of influenza (e.g., pneumonia), or co-morbidities. There were no US deaths that appeared to be related to neuropsychiatric AEs, and no new foreign neuropsychiatric AE-related deaths. There was insufficient clinical information to establish causality in the 13 deaths coded as cardiovascular and in the 6 cases coded with the preferred term 'sudden death'.

A review of the top reported preferred terms (PTs) in the serious crude count reports in pediatric patients shows that neuropsychiatric AE terms and influenza disease-related terms are the most commonly reported PTs; NP AEs are currently labeled either in the Warnings and Precautions or Post-Marketing sections of the label. Assessment of AEs in the ≤ 12 months old infants did not identify any new unlabeled safety concerns; examples of neuropsychiatric AEs in this sub-population included seizures, hallucination, screaming, and restlessness. The AE profile was consistent with the older pediatric age groups.

Data from this review showed that prior to 2008, serious neuropsychiatric AEs in pediatric patients appeared to be reported mostly from Japan; however, from 2008-2009 the number of U.S. reports rose, as did reports from countries other than US or Japan. After the 2009 H1N1 pandemic influenza season, the NP AE reporting decreased through 2011 while leveling off between 2010 and 2011. The reasons for the change in reporting trends for NP AEs are multi-factorial.

This review found no new safety signals in pediatric patients exposed to oseltamivir. DPV recommends routine pharmacovigilance. Given the changing trends in reporting for neuropsychiatric AEs, DPV recommends that consideration be given to removing the text 'mostly from Japan' from the description of neuropsychiatric AEs in the Warnings and Precautions section of the Tamiflu label.

1 INTRODUCTION

1.1 PRODUCT FORMULATIONS AND INDICATIONS

Oseltamivir is approved in the U.S. for the treatment and prophylaxis of influenza in patients 1 year and older. For treatment, it is indicated for uncomplicated acute illness due to influenza in patients who have been symptomatic for no more than 2 days.

It is available as an oral capsule and suspension:

- NDA 21-087: capsules (30, 45, and 75 mg)
- NDA 21-246: 6 mg/mL liquid/suspension

1.2 REGULATORY HISTORY

Oseltamivir was first approved in adults for treatment of influenza in 1999. Use for prophylaxis and treatment of influenza in pediatric patients occurred in 2000 or later. Notable regulatory actions affecting indications in children are listed in Table 1 below.

Table 1: Regulatory Actions for Oseltamivir Affecting Pediatric Labeling

Approval Date	Indication	Population
Oct. 27, 1999	Treatment of influenza	Adults
Nov. 17, 2000	Prophylaxis of Influenza	Adults and pediatrics ≥ 13 years of age
Dec. 14, 2000	Treatment of influenza	Adults and pediatrics ≥ 1 years of age
March 22, 2004	Pediatric exclusivity granted	
Dec. 21, 2005	Prophylaxis of influenza	Pediatrics 1-12 years of age
Apr 26, 2009 – June 23, 2010; Emergency Use Authorization (EUA)	Treatment and prophylaxis of individuals exposed to 2009 H1N1 Influenza	Patients < 1 years old Later time point after symptom onset Hospitalized patients

1.3 PEDIATRIC FILING HISTORY

This review is triggered by pediatric labeling changes to the Clinical Trials Experience section of labeling from February 2010 which added clinical data from two pediatric (1-12 years) studies:

- NV20235: A randomized, controlled, multi-center trial of oseltamivir versus placebo for the seasonal prophylaxis of influenza in immunocompromised patients.

- NV20236: An open label trial for seasonal prophylaxis during influenza season.

1.4 PEDIATRIC LABELING*

- ***Dosage and Administration:***

  TAMIFLU is not indicated for treatment of influenza in pediatric patients younger than 1 year. The safety and efficacy of TAMIFLU for prophylaxis of influenza in pediatric patients younger than 1 year of age have not been established.

- ***Warnings and Precautions:***

  Neuropsychiatric Events: Influenza can be associated with a variety of neurologic and behavioral symptoms that can include events such as hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

  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.

  Cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme have been reported in postmarketing experience with TAMIFLU. TAMIFLU should be stopped and appropriate treatment instituted if an allergic-like reaction occurs or is suspected.

- ***Post Marketing:***

  Psychiatric: Abnormal behavior, delirium, including symptoms such as hallucinations, agitation, anxiety, altered level of consciousness, confusion, nightmares, delusions

  Dermatologic: Rash, dermatitis, urticaria, eczema, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme

1.5 SUMMARY OF OSE ACTIVITIES FOLLOWING THE NOVEMBER 2007 PAC MEETING

In 2007 OSE performed a comprehensive review of 596 cases of neuropsychiatric AEs from the Adverse Event Reports Monitoring System (AERS) database associated with use of oseltamivir for the November 2007 Pediatric Advisory Committee (PAC) meeting. The 2007 review noted a possible association between the use of oseltamivir and the development of neuropsychiatric AEs; however, it concluded there is uncertainty about whether neuropsychiatric events are related to oseltamivir, influenza disease, or a combination of drug-disease expression, 'particularly in pediatric patients'.† Additionally, the 2007 review found no fatalities in the U.S. that were believed to be caused by neuropsychiatric AEs causally related to oseltamivir. The

* Tamiflu Labeling: Revised March 2011.

† Rothstein A; Edwards E; Truffa M. Tamiflu (oseltamivir) – Safety Update on Neuropsychiatric Events; Review of Neuropsychiatric Events with other antiviral products. November 9, 2007.

review recommended further characterization of neuropsychiatric adverse events in the label; and the label was revised to reflect this recommendation in February 2008.

Enhanced pharmacovigilance activities were conducted during the influenza seasons from 2007 to 2011. This included monthly to bimonthly reports of AERS data and periodic review of drug use data for neuraminidase inhibitors oseltamivir and zanamivir. During the 2009 H1N1 influenza pandemic, surveillance of neuraminidase inhibitors was expanded to also include peramivir (temporarily approved for emergency use during the 2009 H1N1 influenza pandemic). No new safety concerns were identified during the 2010-2011 enhanced pharmacovigilance period. Since then, DPV and DAVP agreed to return to routine surveillance for future influenza seasons unless otherwise warranted.

DPV evaluated several other potential safety signals with oseltamivir:

- May, 2009: A review of all AERS reports in infants $\leq$ 12 months exposed to oseltamivir found seizures and hypothermia temporally associated with oseltamivir use. It remains unclear whether seizures resulted from drug exposure, disease, or both. Hypothermia has since been added to the Adverse Events/Postmarketing Experience section of the Tamiflu label.
- September, 2009: AERS cases of reported possible drug-drug interaction between oseltamivir and warfarin were assessed and the evidence was not supportive. The review was prompted by reports from the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom in August 2009 suggesting prolongation of international normalized ratio (INR), and possible cerebrovascular bleeding in patients treated concurrently with oseltamivir and warfarin.
- December, 2009: A review of AERS reports and literature was conducted to evaluate the potential for oseltamivir to prolong the QT interval, given the concern in a draft manuscript that suggested that oseltamivir may potentiate the QT interval prolonging effects of sotalol when used concurrently. Eleven cases of torsades de pointes in patients exposed to oseltamivir were found between 2000 and 2009; however, most reports involved patients with concomitant cardiac disease or concomitant medications known to prolong the QT interval. While the review was not entirely conclusive regarding these concerns, it was recommended that a thorough QT study be performed to assess the potential risk of QT prolongation associated with oseltamivir.
- February, 2010: This review was conducted in view of several AERS reports of acute pancreatitis in patients with influenza virus infection who were treated with oseltamivir prior to or concomitant with peramivir, an investigational antiviral agent. A review of AERS reports, published literature and other sources did not provide substantial evidence of a safety signal for pancreatitis associated with oseltamivir.
- February, 2010: A review of AERS reports was unable to substantiate a safety concern regarding use of oseltamivir in nursing mothers. This review was conducted following a single case of erythema multiforme minor in a 6 month old exposed to oseltamivir via breast milk that was identified during the heightened monitoring of AEs associated with oseltamivir use during the 2009 H1N1 influenza season.

DEPI evaluated several safety signals with oseltamivir during and following the 2009 influenza pandemic. The date of review, topic, and source of data are underlined below, followed by conclusions from the respective reviews.

- November 2009/Warfarin and oseltamivir drug interaction/ Medicare Part D Data: "Within the limitations of the data, we did not find evidence to support an interaction between oseltamivir and warfarin resulting in increased bleeding events among Medicare beneficiaries."
- April 2010/Surveillance for hemorrhagic colitis AEs/Medicare Part D and Department of Defense Data: Surveillance data from Medicare Part D and the Department of Defense was inadequate to support an association between use of oseltamivir and hemorrhagic colitis or intestinal perforation, although the review mentioned that "clearly such events can occur with oseltamivir use."
- January 2011/Neuropsychiatric AEs/Review of Japanese Ministry of Health Labor and Welfare (MHLW) Epidemiological Study: The study report concluded, "…the results do not go so far as to show that there is a significant, positive correlation between the use of oseltamivir and abnormal behavior," but the results "do not directly indicate that there is no relationship between the use of oseltamivir and abnormal behavior."
- February 2011/Neuropsychiatric AEs with anti-influenza drugs/Federal Partners Collaboration databases: In the four databases examined (Medicare, Medicaid, VA, DoD), there was no obvious signal for neuropsychiatric illnesses diagnosed following use of oseltamivir; however, the review mentioned that "the limitations of the analyses must be borne in mind."

The Division of Medication Error Prevention and Analysis (DMEPA) conducted several reviews resulting in regulatory actions due to medication errors associated with use of oseltamivir. Dosing errors were noted with the then available 12 mg/mL liquid formulation of oseltamivir, which led to removal of the 12 mg/mL formulation and replacement by a 6 mg/mL formulation. DAVP and DMEPA collaborated with Roche to revise the concentration of the commercially prepared oral suspension from 12 mg/mL to 6 mg/mL, and the measurements for the oral dosing device from milligrams (mg) to milliliters (mL).

2 METHODS AND MATERIALS

As further delineated in section 2.2 below, our preliminary search of AERS reports received for the specified period (June 1, 2007 through December 31, 2011) found 902 serious pediatric (0 to 16 years) adverse event reports. The large number of reports precluded individual review of each report. Therefore, we employed the following review strategy in addition to our review of all unique pediatric death reports (N=112) and all unique infant (≤12 months) serious outcome reports (N=42):

- We performed data mining of AERS data for *all* adverse event outcomes reported in AERS (serious and non-serious) in children up to and including 16 years in order to identify any new safety concerns.
- Additional activities included assessing:
    - AERS Crude Data (N=902) for the following (See Section 2.2 below):
        - Top reported PTs for all serious pediatric reports

- Top reported PTs for serious pediatric neuropsychiatric[‡] reports

- AERS crude counts for nervous system disorders SOC and psychiatric disorders SOC by country of report (US, Japan, Other) and year
- AERS crude counts for neuropsychiatric AEs[‡] by country of report (i.e., US, Japan, Other) across reporting years to assess geographic differences in reporting

2.1 DATA MINING SEARCH STRATEGY: PEDIATRIC (0 TO 16 YEARS) ADVERSE EVENTS WITH OSELTAMIVIR STRATIFIED BY AGE

We performed data mining of AERS data in order to identify potential safety signals. This strategy would identify all AEs (serious and non-serious) with elevated EB05 scores (≥2) signifying potential safety issues. Data mining was stratified by age groups from 0 to 16 years, including subgroups 0 to 1 year, 2 to 5 years, 6 to 11 years, and 12 to 16 years.

This reviewer conducted an AERS–based data mining analysis of oseltamivir with Empirica™ Signal 7.0 applying an EB05 ≥ 2 stratified by age, with a data refresh date of March 22, 2012. Elevated EB05 scores (≥2) show that any particular preferred term is reported in a greater proportion with a particular drug than with other drugs (i.e., greater than expected). This elevated EB05 score indicates that a drug-event pair has disproportionally more reports in the database than did this event in association with other drugs in the database. **Note that the EB05 score measures relative reporting of various events among all drugs in the database and that an elevated EB05 does not imply causality between the drug and event of interest.**

2.2 AERS SEARCH STRATEGY

The AERS search strategies for identifying adverse event reports are outlined in Tables 2 and 3 below. We first searched for all adverse event reports in AERS (Table 2). We then searched for reports associated with neuropsychiatric AEs (Table 3).

Table 2. AERS Search Strategy*	
Date of search	January 15, 2012
Time period of search	June 1, 2007^ – December 31, 2011
Product Terms	Oseltamivir and related names

* See Appendix D for description of the AERS database.
^ Date since last AERS review of neuropsychiatric AEs with oseltamivir presented at the 2007 PAC

Table 3. AERS Search Strategy* Neuropsychiatric Adverse Events	
Date of search	January 15, 2012
Time period of search	June 1, 2007^ – December 31, 2011
Product Terms	Oseltamivir and related names
MedDRA Terms	Refer to Appendix B

* See Appendix D for description of the AERS database.
^ Date since last AERS review of neuropsychiatric AEs with oseltamivir presented at the 2007 PAC

‡ See Appendix B for list of MedDRA terms used

3 RESULTS

3.1 DATA MINING (0 THROUGH 16 YEARS)

Table 4 below shows all preferred terms (serious and non-serious) with EB05 scores of at least 2 in patients 0 to 16 years. The majority of PTs are labeled terms (e.g., hallucinations, pathogen resistance, and abnormal behavior), closely related to labeled terms (e.g., auditory hallucinations, depressed level of consciousness - labeled as 'altered level of consciousness'), unrelated (e.g., caesarean section), or do not report an event (e.g., 'no adverse event').

Table 4: Preferred Terms for Oseltamivir in AERS with Elevated Disproportionality Scores (≥2.0), Stratified by Age*

Age Stratum(yrs)	*Preferred Term (n)*	*Actionable Signals*
0-1	Caesarean section (29), Hallucination (6), Incorrect dose administered (10), No adverse event (32), Normal newborn (35), Pathogen resistance (6), Incorrect storage (3)	None
2-5	Abnormal behavior (80), Delirium (23), Hallucination (32), Nightmare (15), Hypothermia (14), No adverse event (36), Pathogen resistance (9), Sudden death (9)	None
6-11	Abnormal behavior (161), Confusional state (23), Delirium (53), Depressed Level of Consciousness (19), Pathogen Resistance (6), Delirium febrile (6), Hallucination (82), Hallucination auditory (15), Hypothermia (10), Nightmare (20), No adverse event (21), Sleep terror (10)	None
12-16	Abnormal behavior (100), Hallucination (42), Confusional state (21), Delirium (22), No adverse event (11), Delusion (10), Depressed level of consciousness (17), Pathogen Resistance (6)	None

*Datamining scores are found in Table C1 in appendix C of this document.

3.2 AERS REPORTS

Table 5: Crude counts[1] of AERS Reports from All Sources From FDA Receive Date June 1, 2007 to December 31, 2011			
	All reports (US)[2]	Serious[3] (US)	Death (US)
Adults (≥ 17 yrs.)	2105 (338)	1473 (268)	470(38)
Pediatrics (0-16 yrs.)	1139 (325)[4]	902 (241)	115 (12)[5]
Age unknown (Null values)	883 (166)	362 (92)	90 (9)[5,6]
Total	4127 (829)	2737 (601)	675 (59)

[1] May include duplicates
[2] US counts in parentheses
[3] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events
[4] See Figure 1
[5] See Figure 4
[6] 7 of these deaths were in children

Figure 1. Total Number of Pediatric Reports (including serious and non-serious) for Oseltamivir, by year of FDA receipt (June 1, 2007 through December 31, 2011) (n=1139)

These numbers include data where age (0-16 years) is known and may contain duplicate reports.

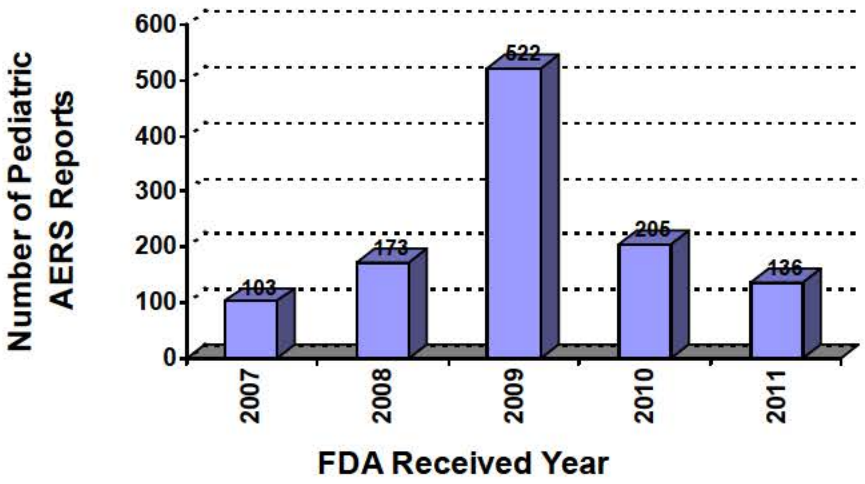
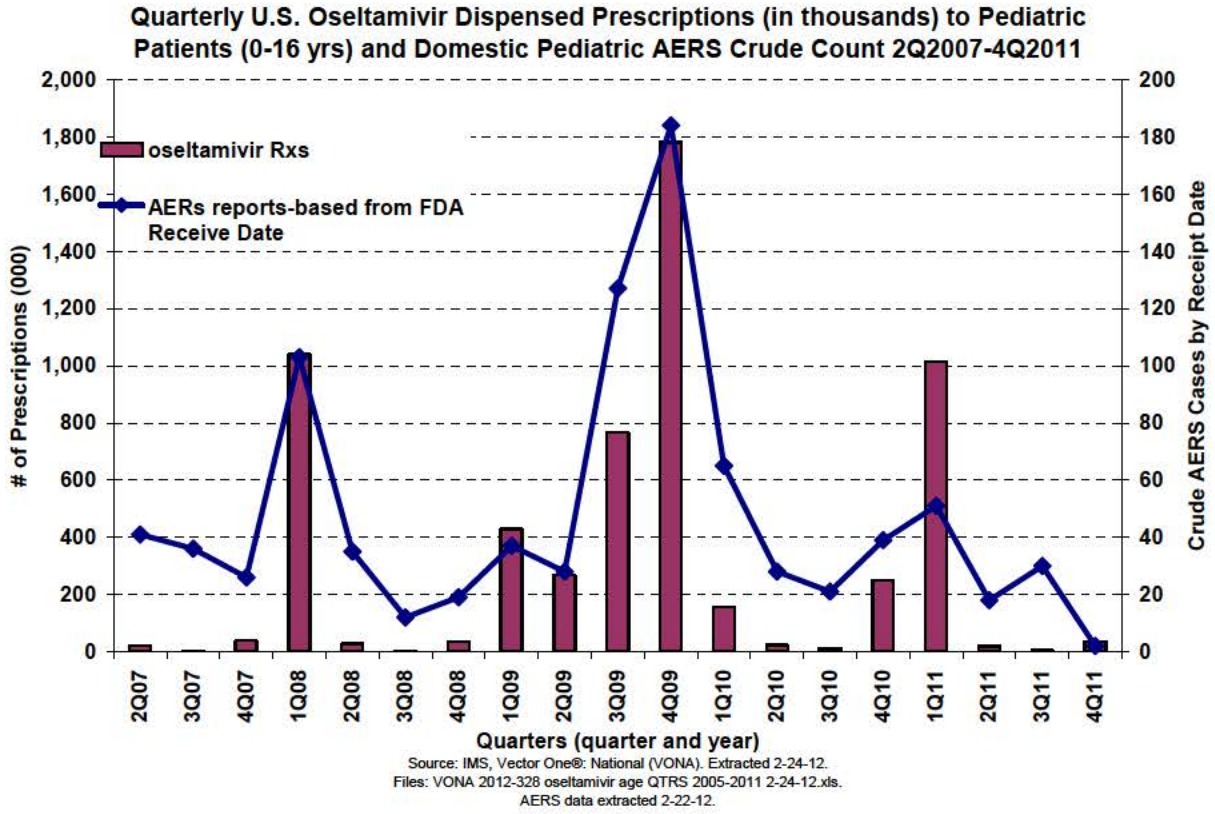


Figure 2 below shows the quarterly trend of domestic pediatric AERS reports closely mirrors the domestic prescriptions dispensed to pediatrics for oseltamivir; with a peak corresponding with the 2009 pandemic.



3.3 Top Reported Preferred Terms (PTs) From a Crude Count of Serious Pediatric (0 to 16 years) Adverse Event Reports for Oseltamivir (N=902)

Table 6 below lists the top reported PTs from the serious pediatric adverse event reports for oseltamivir. We note that neuropsychiatric terms and influenza disease related terms are the most commonly reported PTs. NP AEs are currently labeled. Sixty-five of the 902 reports included in this crude count are follow up cases, initially reported to FDA prior to June 1, 2007.

Table 6: Top reported Preferred Terms of Serious Pediatric (0 to 16 years) Adverse Events for Oseltamivir (FDA Report Received Date: June 1, 2007 through December 31, 2011) (N=902, crude count)		
Preferred Term (PT)	*Count of PT*	*Percentage of Total*
Abnormal behaviour	234	25.94
Hallucination	110	12.2
Vomiting	64	7.1
Convulsion	63	6.98
Delirium	61	6.76
Confusional State	51	5.65
Aggression	37	4.1
Nightmare	37	4.1
Agitation	32	3.55
Pneumonia	31	3.44
Pathogen Resistance	27	2.99
Pyrexia	25	2.77
Drug Ineffective	23	2.55
Maternal Exposure During Pregnancy*	23	2.55
Crying	22	2.44
Diarrhea	22	2.44
Hallucination, Visual	22	2.44
Nausea	21	2.33
Screaming	20	2.22
ARDS	19	2.11
Respiratory Failure	18	2

* 'Maternal Exposure During Pregnancy' may be reported in higher frequency given the Agency's request to Roche in May 2009 to submit all serious and non-serious reports with pregnant woman

3.4 TOP REPORTED PTS FROM A CRUDE COUNT OF SERIOUS PEDIATRIC (0 TO 16 YEARS) NEUROPSYCHIATRIC§ AE REPORTS FOR OSELTAMIVIR (N=600)

Table 7 below reports the top PTs associated with neuropsychiatric AEs from serious pediatric reports for oseltamivir. The majority of PTs are labeled in the Warnings and Precautions or Post-Marketing sections of the label, or are closely related to labeled terms. The unlabeled terms include aggression, visual hallucination, screaming, fear, auditory hallucination, anger, and somnolence. Of note, each of the 600 reports may include multiple preferred terms across multiple System Organ Classes (SOCs).

§ See Appendix B for list of MedDRA terms used

Table 7: Top reported Preferred Terms from Serious Pediatric (0 to 16 years) *Neuropsychiatric*[§] AE Reports for Oseltamivir (FDA Report Received Date June 1, 2007 through December 31, 2011) (n=600, crude count)		
Preferred Term (PT)	*Count of PTs*	*Percent of Total*
Abnormal behavior	234	39
Hallucination	110	18
Convulsion	63	10.5
Delirium	61	10.17
Confusional State	51	8.5
Vomiting	44	7.33
Aggression	37	6.17
Nightmare	37	6.17
Agitation	32	5.33
Crying	22	3.67
Hallucination, visual	22	3.67
Screaming	19	3.17
Encephalopathy	17	2.83
Insomnia	17	2.83
Anxiety	15	2.5
Fear	15	2.5
Pyrexia	15	2.5
Disorientation	14	2.33
Hallucination, auditory	14	2.33
Sleep Terror	14	2.33
Anger	13	2.17
Diarrhea	13	2.17
Headache	13	2.17
Nausea	13	2.17
Dizziness	12	2
Loss of Consciousness	12	2
Somnolence	12	2

§ See Appendix B for list of MedDRA terms used

FDA Reviewer Comments: Overall, a review of top PTs from crude counts of serious pediatric adverse event reports (Table 6) and more specifically neuropsychiatric AEs (Table 7) did not identify any new safety concerns. The current Tamiflu label describes these AEs adequately.

3.5 NEUROPSYCHIATRIC AE REPORTS IN PEDIATRIC (0 TO 16 YEARS) AGE GROUPS FROM A CRUDE COUNT OF AERS REPORTS FOR OSELTAMIVIR BY YEAR

Figure 3 displays trend data for crude counts of pediatric AERS reports of Nervous System Disorders SOC and Psychiatric Disorders SOC with oseltamivir. Up through 2007, Japanese reports represented the majority of pediatric neuropsychiatric reports in AERS. From 2008-2011 the number of US reports rose, initially possibly due to stimulated reporting after NP labeling changes in 2008, and subsequently, possibly due to increased drug use during the 2009 H1N1

influenza pandemic. Concurrently, the number of Japanese reports began to decrease; while this may be due to Japan's restricted use in the pediatric age group, Japanese drug use data is unavailable, which limits our ability to draw conclusions.

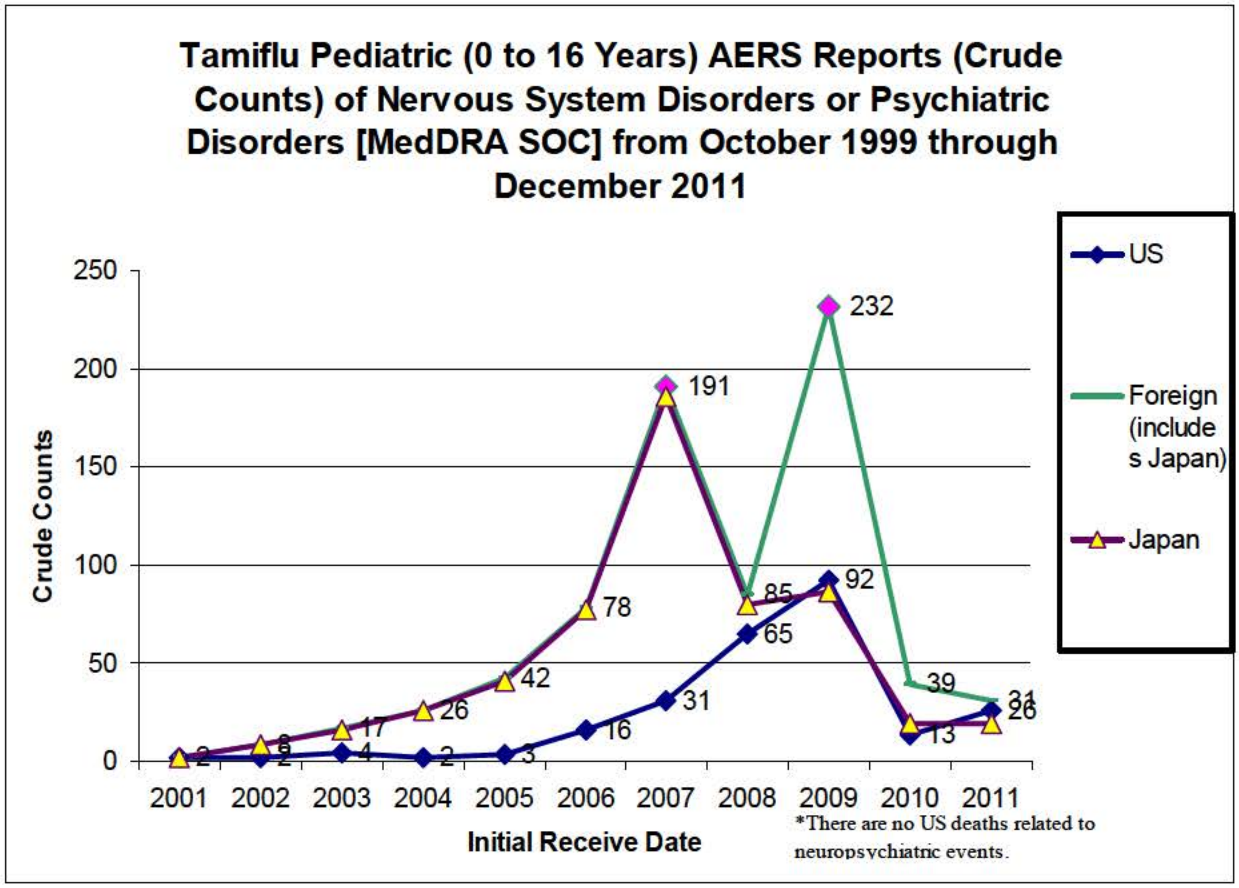


Table E1 in the appendix displays crude counts of AERS reports for serious neuropsychiatric adverse events by year and country of origin (i.e., US, Japan, and other); those data support the graphical display in Figure 3. Table E1 also shows an increase in serious pediatric neuropsychiatric reports from foreign countries (other than Japan) since the 2009 H1N1 pandemic. Crude AERS data for serious pediatric neuropsychiatric AE reports (0 to 16 years) for oseltamivir show that the number of pediatric reports relative to all ages remained relatively stable after the 2009 H1N1 influenza pandemic (also see Appendix E). The proportion of serious pediatric neuropsychiatric AE reports compared to all pediatric reports trended down since 2008.

FDA Reviewer Comment: Based on AERS data, it appears that there is no particular geographic specificity for neuropsychiatric adverse event reports in pediatric patients.

3.5.1 Selected Cases of Interest from US Neuropsychiatric Adverse Events 2010 to 2011

There were 26 US cases of neuropsychiatric AEs in pediatric patients from 2010 to 2011 (two cases were excluded: one case was in an adult, and the other was a case of influenza encephalopathy described in section 3.7.2 below). Of the 26 reports, 24 reported use of oseltamivir for influenza treatment, 1 for influenza prophylaxis, and 1 for an off-label use. The

majority of cases were confounded by influenza complications and other co-morbidities, and no new safety signals were identified.

The average age was 6 years with a range from 2 months to 16 years. There were 13 females and 13 males.

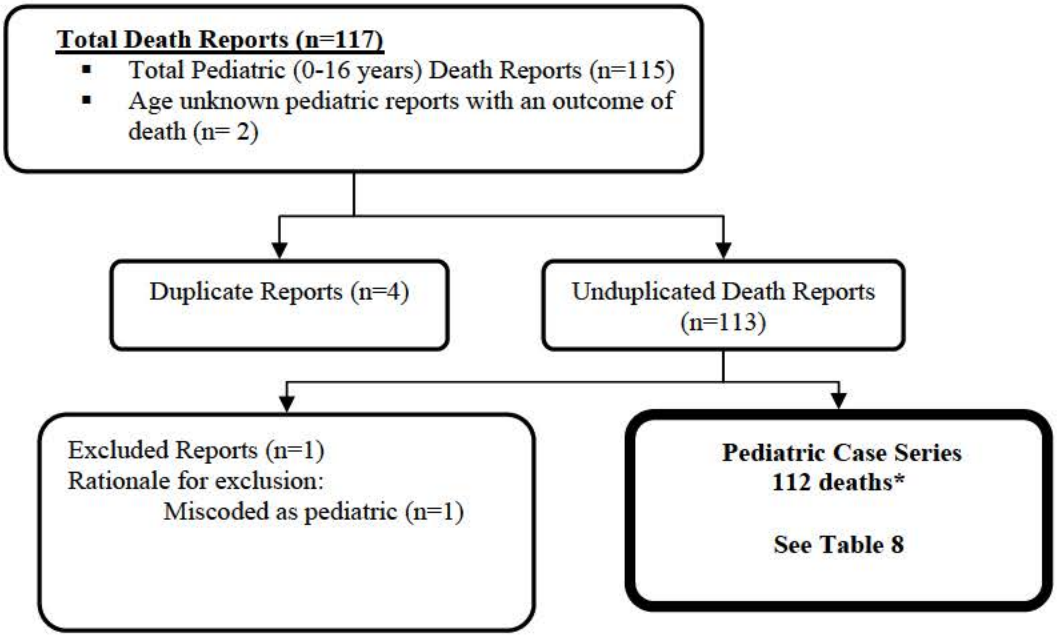
Representative case vignettes of the non-fatal cases are provided below:

- ISR # 7600575/US/October 2009: This consumer report describes a 10 year old male who experienced "ill-defined" movement disorder after receiving twice daily oral oseltamivir 30 mg for influenza ***prophylaxis***. The report describes difficulty standing up and swallowing, "repetitive movements" and eyes rolling back after taking oseltamivir for influenza prophylaxis. On an unspecified date, he received an influenza vaccine, symptoms worsened and it was again reported that he couldn't swallow or perform activities of daily living such as dressing, and he subsequently lost 20 pounds. He was seen by a neurologist and received therapy with glutathione and divalproex sodium (Depakote). Additional clinical information was not reported.
- ISE # 7365835/US/March 2011: This consumer report describes a 6 year old female who reportedly experienced visual and auditory hallucinations intermittently for approximately 20 hours after receiving 8 days of oseltamivir for influenza ***prophylaxis***. It was reported that the patient did not have a fever during this incident and continued to hear voices once oseltamivir was discontinued. Additional clinical information was not reported.
- ISE # 6618772/US/February 2010: This consumer report describes a 16 month old female who experienced agitation, crying, and possible disequilibrium during ***treatment*** with oseltamivir. She reportedly returned to her baseline status 12 hours after her last oseltamivir dose. Additional clinical information was not reported.

3.6 FIGURES 4 AND 5 PEDIATRIC DEATHS AND SERIOUS INFANT (≤ 12 MONTHS) AE CASES

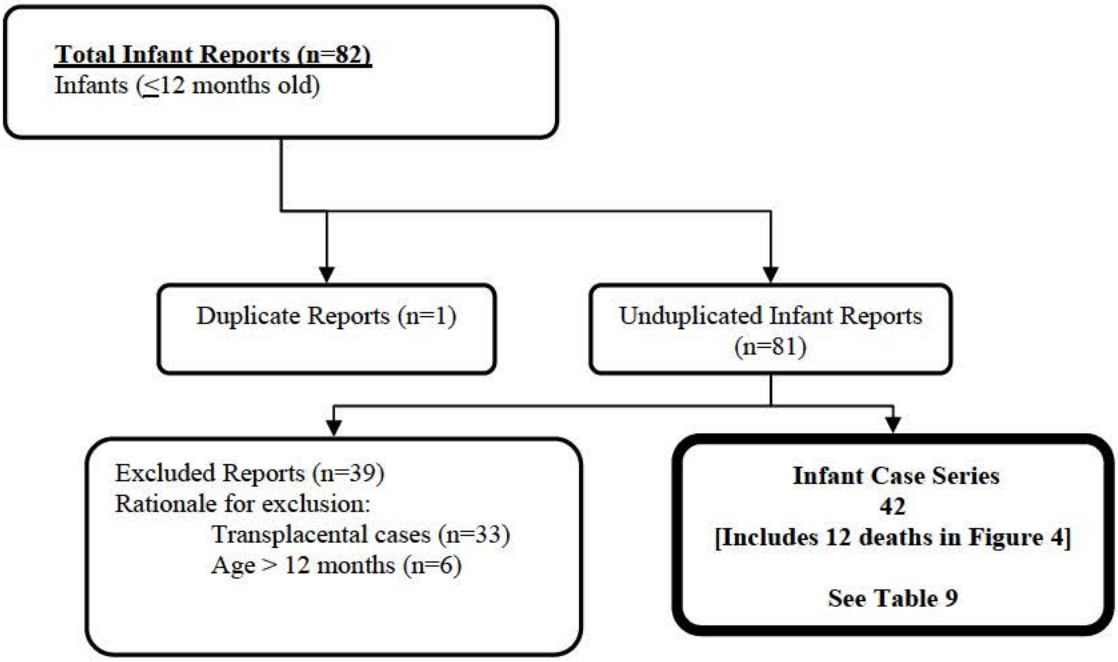
Figures 4 and 5 below delineate, respectively, selection criteria for the pediatric death cases and cases in infants ≤ 12 months old.

Figure 4: Pediatric Death Cases



**Includes 2 reports with a null age and outcome of death describing pediatric patients.*

Figure 5: Infant (≤12 months) Cases



3.7 PEDIATRIC DEATH CASE SERIES (N=112)

3.7.1 Descriptive Characteristics from Pediatric Death Case Series (N=112)

Table 8 below shows descriptive characteristics from the pediatric deaths.

Table 8: Case Characteristics of Pediatric (0 to 16 years) Death Case Series. [FDA Receive Date June 1, 2007 through December 31, 2011] (N=112)	
Age (years) (n=110)	Average (6.8) Median (5.0) Range (22 days to 16 years)
Gender	Male (63) Female (48) Unknown (4)
Report Origin	United States (11) Japan (38) Other Foreign (63) Not reported (0)
Adverse Event date (n=85)	2002 (2) 2008 (2) 2005 (5) 2009 (50) 2006 (4) 2010 (14) 2007 (5) 2011 (3)
Time to onset from first dose of oseltamivir to death (days)	Average (7.8) Median (3) Range (0 to 58)
Duration of therapy (days) (n=25)	Mean (3.8) Median (2) Range (1 to 12)
Indication for Use Hospitalization Co-infection with pneumonia Report of concomitant antibiotic therapy	Treatment (109) Prophylaxis (3) Yes (95) Not Reported (17) Yes (39) Not Reported (73) Yes (25) Not Reported (87)
Reported Co-morbidities	Lung Disease (5) Malignancy (9) Prematurity or Developmental Delays (5) Other (12) Not Reported (80)
Reporter attribution for cause of death (each report may include ≥1 term)	Neuropsychiatric adverse event (3) Multi-organ Failure (9) Cardiovascular (13) Sudden Death* (6) Influenza encephalopathy (15) Pathogen Resistance/Drug Ineffective (13) Primary Respiratory cause (52) Reporter Attribution not provided (12)
* 'Sudden Death' – these cases were coded with the preferred term 'sudden death' with or without autopsy findings	

3.7.2 Pediatric Cases with a Reported Outcome of Death (n=112)

The 112 death cases include 7 follow up reports that were initially received prior to June 1, 2007. As a result, there is some overlap with the cases previously discussed in the 2007 OSE review. Additionally, 18 cases reported an adverse event date prior to June 2007 (range 2001 through 2007).

Foreign cases, not including Japan, comprised the largest proportion of deaths in this case series. The most common country of origin was Japan (n=38), followed by US (n=11). Indication for use was most commonly for treatment (n=109), not prophylaxis (n=3).

Each pediatric death case was individually reviewed. Most cases were confounded by co-morbidity, and distinguishing drug-event causality with oseltamivir was not possible. No US death reports were attributed to oseltamivir. There were 11 US deaths in pediatric patients, only two of which reported prophylactic use of oseltamivir. The cause of death in these two cases was not attributed to oseltamivir but other medical conditions (i.e., surgical complications and disseminated tuberculosis). The remaining death reported during prophylactic oseltamivir use was a foreign report of a 15 year old female from July 2009. She had two negative influenza tests and was discharged after a short hospitalization for assessment of influenza and pneumonia. Discharge medication included antibiotics for pneumonia and oseltamivir for influenza prophylaxis. One to two days after hospital discharge, she experienced septic shock and cardio-respiratory arrest with failed resuscitation efforts and died upon discharge.

Eighty-five percent (95/112) of the pediatric patients in this case series required hospitalization, 50% (57) required ICU admission, and 38% (n=43) required ventilation. Thirty-five percent (n=39) reported co-infections such as pneumonia, including bacterial pneumonia. The most common reporter attributed causes of death were: primary respiratory cause (n=52), pathogen resistance (n=13), influenza encephalopathy (n=15), cardiovascular causes (n=13) and reports coded as 'sudden death' (n=6, with or without reported autopsy findings). No deaths were related to hypersensitivity or skin reactions.

Of fifteen deaths attributed to influenza-related encephalopathy, there was a single US case reported in a 3.5 year old male who received two doses of oseltamivir and experienced hallucinations, encephalitis, and abnormal behavior. It is unknown if an autopsy was performed and no additional information was provided (ISR # 7320791).

There were three neuropsychiatric related deaths ascribed to trauma (i.e., falls) during oseltamivir treatment, and were previously reported and reviewed in the 2007 OSE review and are reflected in current labeling.[**] There have been no new reported death cases causally related to neuropsychiatric AEs since the 2007 review.

In the remainder of the death cases, deaths appeared to be directly attributable to influenza and its complications; a line listing of the cases are located in Appendix F.

Cases attributed to have 'Cardiovascular' causes of death (n=13) and cases coded with the PT 'Sudden Deaths' (n=6):

All 19 cases were for treatment of influenza and required hospitalization. Co-morbidities were not always reported. Based on available data, causality between administration of oseltamivir

[**] Rothstein A, Edwards E, Truffa M. Tamiflu (oseltamivir) – Safety Update on Neuropsychiatric Events; Review of Neuropsychiatric Events with other antiviral products. November 9, 2007.

and AEs could not be established, and the contribution of influenza disease-related complications to these AEs could not be ruled out. Note: the cardiovascular deaths described below are based on reporter attributions for cause of death whereas the 'sudden death' reports are based on MedDRA coding of the PT 'sudden death.' These cases are summarized below (identified by ISR #, country of origin, and event date).

Cardiovascular (n=13):

- ISR # 5907700/Japan/March 2007: A 3 year old male died due to cardio-respiratory arrest during the use of oseltamivir for influenza A treatment. His medical history was pertinent for febrile convulsions and negative for cardiovascular, cerebrovascular and respiratory disease. Three hours after taking his first dose of oseltamivir, the patient was found in asystole and confirmed dead. The reporter stated that it is unknown whether sudden infant death syndrome had occurred, though by definition, this is unlikely. Relation of this AE to oseltamivir is reported as unknown.
- ISR # 6316850/Israel/August 2009: A 12 year old female patient experienced cardiac arrest while on oseltamivir for 2009 H1N1 influenza. She was concurrently taking antibiotics for pneumonia. Four days after the patient was discharged from the hospital she suddenly developed cardiac failure, and respiratory arrest and died. It was reported that there was no connection between the use of oseltamivir and death. Additional clinical information is unavailable.
- ISR # 6327564/Great Britain/August 2009: A 14 month old female with pulmonary atresia experienced occlusion of a Blalock-Taussig (BT) shunt and cardiac arrest while receiving oseltamivir for an unknown indication. Concomitant medications included aspirin. It was reported that the blocked shunt was possibly related to hyper-coagulation. The reporter did not provide an assessment of causal relationship between oseltamivir and shunt occlusion/fatal cardiac arrest.
- ISR # 6359767/India/September 2009: A 16 year old male experienced a pneumothorax and a 'heart' infection after finishing a 5 day course of oseltamivir for the treatment of 2009 H1N1 influenza. Suddenly, he developed a pneumothorax and 'heart infection' and died 17 days after initiating oseltamivir. The report provided no assessment of causality or further clinical information.
- ISR # 6437298/Japan/October 2009: A 8 year old female experienced cardiac failure, convulsions and went into cardiopulmonary arrest while receiving oseltamivir for 2009 H1N1 Influenza on day 1 of therapy. The reporter assessed the cause of cardiac failure to be unrelated to oseltamivir. Additional clinical information is not available.
- ISR # 6483168/Japan/November 2009: A 2 year old male patient with 2009 H1N1 influenza 'died of progression of underlying disease while receiving treatment with oseltamivir' and while in cardiopulmonary arrest on day 1 of oseltamivir therapy. It was reported that the patient had no pertinent medical history to report. Additional clinical information is not available.
- ISR # 6291037/US/September 2008: A 12 year old female with cerebral palsy, fever, hypovolemic and septic shock, upper GI bleed, pneumothorax and ARDS had progressive clinical decline due to underlying sepsis and died. She experienced pneumonia and was transferred to the ICU with upper GI bleeding and respiratory failure. She required intubation and ventilation. One week later she was positive for influenza A

and started on oseltamivir. On an unspecified date, the patient experienced cardiac arrest with respiratory failure and the patient died. An autopsy was performed. The investigator thought the ARDS could be related to oseltamivir. Family declined CPR.

- ISR # 7179665/Thailand/January 2004: A 7 year old male who became infected with avian influenza virus, initially developed mild influenza symptoms. His illness progressed to ventilator dependency, pneumonia, elevated liver enzymes, and cardiac dysfunction requiring inotropic support. Oseltamivir was given but the patient succumbed to progressive respiratory disease. The report states there is limited information to establish a causal link between oseltamivir and any of the AEs leading to death.
- ISR # 5821856/Japan/February 2005: A 33 month old male died due to hypoxic organ failure resulting from sudden cardiopulmonary arrest after experiencing hypothermia. Past medical history was unremarkable. He received one dose of oseltamivir for treatment of influenza A, along with single doses of cyproheptadine, carbocysteine, and tipepidine hibenzoate. After a brief nap he reported a headache and experienced approximately 1 hour of inconsolable crying. One to two hours later, shortly after a parent reported witnessing spontaneous sleep movements, the patient was found flaccid and not breathing. He was resuscitated and 28 hours later he died due to hypoxic organ failure. The reporter considered cardiopulmonary arrest to be due to oseltamivir; however, an autopsy was not performed.
- ISR # 6446287/Japan/November 2009: A 5 year old female patient with 2009 H1N1 influenza and fever to 40^{o}C experienced influenza disease progression and a convulsion, after which she was prescribed oseltamivir. Two hours later she was in cardiopulmonary arrest. Resuscitation efforts failed and she was pronounced dead. Reporter attributed the cause of death as unknown but suspected 2009 H1N1 influenza as the cause of death.
- ISR # 6583203/Japan/February 2010: A 15 year old male receiving oseltamivir for treatment of 2009 H1N1 influenza experienced suspected cardiopulmonary arrest at home. He was resuscitated and transported to an ICU for treatment. He died after an extended ICU stay. Death was attributed to acute myocarditis unrelated to oseltamivir.
- ISR # 7762145/Japan/January 2011: A 9 year old male with a history of cardiac disease (not specified), developmental delay, and deafness presented with symptoms related to influenza B and was treated with oseltamivir (dose and duration not specified). Two days later he was found in cardio-pulmonary arrest and died. Concomitant medicines included sodium valproate and sodium picosulfate. Cause of death was cardiopulmonary arrest. Causal relation to oseltamivir was reported as unknown.
- ISR # 6437296/Japan/October 2009: A 6 year old female experienced progression of influenza disease including cardiac arrest while on oseltamivir for 2009 H1N1 influenza. Resuscitation failed and she died. The reporter stated that the direct cause of death was unknown but that the progression of the underlying disease was not related to oseltamivir.

<u>'Sudden Death' (n=6):</u>

- ISR # 5520981/Japan/March 2005: A 4 year old female suddenly died due to suspected myocarditis. She began oseltamivir 3 days after the onset of influenza-like symptoms. On day 2 of treatment, she developed cardio-respiratory arrest and did not respond to resuscitation. Reporter attribution for cause of death: myocarditis.

- ISR # 5520984/Japan/December 2002: A 2 year old male experienced cardiac arrest and died. He had varicella infection, 'pseudo-croup', and influenza infection. He developed breathing difficulties leading to intubation. Reporter attribution for cause of death: influenza encephalopathy. A second reporting physician stated that the cause of death was suspicion of myocarditis due to Influenza A, and a causal relationship between the death and treatment with oseltamivir was unlikely.
- ISR #6541555/Japan/October 2009/Literature report: A 5 year old patient with H1N1 influenza experienced pneumonia and acute myocarditis while on oseltamivir for influenza treatment. Reporter attribution for cause of death: Confirmed as severe pneumonitis and acute myocarditis.
- ISR # 5521007/Japan/December 2005: A 7 year old male with Down's syndrome and porencephaly experienced cardiopulmonary arrest, low platelets ($24.4 \times 10^4/mm^3$), hemorrhage of digestive tract, and sudden death. He experienced cardiopulmonary arrest and died on day 1 of oseltamivir therapy. The reporter stated that attribution of death to oseltamivir was unlikely given the patient's co-morbidity, receipt of only 1 dose, and further stated that the relationship of gastrointestinal bleeding to oseltamivir could not be determined since the patient had pre-existing diarrhea.
- ISR # 5794968/Japan/December 2002/Literature report: A 3 year old male experienced respiratory arrest and sudden death during sleep while receiving oseltamivir for influenza treatment. Autopsy showed congestion and swelling of the brain, histological findings compatible with bronchitis which was felt to be due to 'typical' influenza virus infection, as well as lung congestion ascribed to sudden cardiac arrest. Reporter attribution: Reporter considered sudden death to be related to oseltamivir, but also stated that the autopsy findings were 'consistent with influenza-induced cerebral disease'.
- ISR # 6521427/Japan/Event date not reported: A 5 year old male experienced respiratory depression and sudden death after his second dose of oseltamivir for 2009 H1N1 influenza. Reporter attribution: The reporter assessed the AEs of sudden death and respiratory depression as related to the use of oseltamivir; autopsy was not performed.

Influenza Encephalopathy (n=15): These death reports originated from Japan (n=13), France (n=1) and the United States (n=1). The adverse event dates range from 2008 to 2011, with the majority (n=9) reported during the 2009 H1N1 Influenza Season. The age range is from 1 year to 16 years with an average of 6.1 years. Eleven case reports attribute the cause of encephalopathy to influenza or note that the etiology is unrelated to oseltamivir, two reports attribute death due to complications of Reye syndrome, one death case reports encephalopathy but attributes death to multi-organ failure, and the final US case did not report a cause of death. The US case of encephalopathy was described in section 3.7.2 above.

3.8 DESCRIPTIVE CHARACTERISTICS FROM INFANT CASE SERIES - 0 TO ≤ 12 MONTHS (N=42)

Table 9 below summarizes the 42 AERS cases of serious AEs in infants (0 through 12 months old) exposed to oseltamivir (not currently labeled in those < 12 months, since expiration of the EUA discussed above).

Table 9: Case Characteristics of Serious AEs in Infants ≤ 12 months old. [FDA Receive Date: June 1, 2007 through December 31, 2011] (N=42)	
Age(months) (n=42)	Average (7.8) Median (8.9) Range (0.7 to 12)
Gender	Male (23) Female (12) Unknown (7)
Country of occurrence	United States (16) Japan (8) Great Britain (4) Other Foreign (14) Unknown (0)
Adverse Event date (n=17)	2003 (1) 2006(1) 2007(1) 2008 (1) 2009 (13)
Duration of therapy (days) (n=25)	Mean (3.8) Median (2) Range (1 to 12)
Primary Outcome[1]	Death (12) Hospitalized (8) Disability (0) Life-threatening (1) Other serious (21) Congenital anomaly (0) Unknown (0)
Use of Oseltamivir[2]	Prophylaxis (4) Treatment (28) Not Reported (10)

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

[2] Because dose information was not uniformly reported, it is not included in this table.

3.8.1 Infants ≤ 12 months old (n=42)

We reviewed serious AE reports of infants ≤12 months who received oseltamivir for treatment of influenza. Oseltamivir is not currently labeled for use in those < 12 months old; however, this is a vulnerable population and off-label use may take place in clinical practice. Oseltamivir use guidelines for this population were temporarily established through an Emergency Use Authorization (EUA) during the 2009 H1N1 pandemic.

There were 42 cases of serious AEs in infants ≤ 12 months old. Sixteen of 42 cases were reported in the US. Twelve of the 42 reports were fatal. These fatalities were discussed in the pediatric deaths discussed in section 3.7. As stated in section 3.7, these deaths were unrelated to oseltamivir or confounded by significant co-morbidities which limited the assessment of drug-event causality. Co-morbidities included influenza encephalopathy, acute necrotic encephalopathy, prematurity, renal disease, and co-infection. There were also four cases of pathogen resistance; two of which reported prophylactic use of oseltamivir but the causes of death were unrelated to oseltamivir (i.e., surgical complication and disseminated tuberculosis). Three of the 12 infant deaths were reported in the US (one pathogen resistance and two prophylaxis cases, described in section 3.7 above).

Among these 42 cases, the most common AEs were related to the nervous system (n=17; 7 of which were US reports). Reports included seizure, abnormal behavior (i.e. violent, banging head), hallucination, screaming, anxiety, restlessness, sleep disorder, psychotic disorder, and depressed level of consciousness, all of which are labeled or closely related to labeled terms. In summary, neuropsychiatric AEs and seizures were reported with oseltamivir use in patients ≤12 months. There were no reports of death causally associated with neuropsychiatric AEs in patients ≤ 12 months old. Overall, the cases provided limited clinical information and it is unclear whether the AEs resulted from drug exposure, disease, or both. The cases were

confounded by concomitant medications or co-morbid conditions, and a drug-adverse event causality assessment was limited because of insufficient information.

Most of the other reported AEs are currently labeled, and include 6 reports of gastrointestinal related AEs (i.e. diarrhea, vomiting, flatulence, blood streaked stool, bloody diarrhea, increased liver function tests, etc.), four reports of rash, and other miscellaneous (i.e. drug ineffective.

4 DISCUSSION

This review was performed in order to provide an update to the 2007 OSE review for the prior 2007 PAC. We undertook this analysis to evaluate oseltamivir's safety profile by incorporating data mining, reviewing AERS reports of death cases, reviewing all serious infant AERS cases (including deaths), and describing NP AE reports. Given the past history of NP AEs safety reviews with oseltamivir and its presentation at previous PACs, we sought to address reporting trends for NP AE by year and country from June 1, 2007, through December 31, 2011. We additionally assessed if there were any new deaths as a result of NP AEs since the 2007 PAC. On employing the preceding strategy, no new safety signals were identified.

The 2007 OSE PAC review focused on neuropsychiatric AEs with neuraminidase inhibitors (zanamivir and oseltamivir), amantadine, and rimantidine, and found no cases of neuropsychiatric AEs associated with oseltamivir use for either prophylaxis or treatment in adult or pediatric patients where causality could be established. The 2007 OSE review also noted that there continued to be uncertainty about whether neuropsychiatric AEs in patients treated with oseltamivir are manifestations of disease, drug, or a combination of both. At that time, recommendations were made to add fatalities as a result of neuropsychiatric AEs. The product labeling was subsequently revised to reflect that recommendation as well as other revisions (e.g., disease may cause neurologic and behavioral symptoms, estimates of frequency of NP AEs can not be made, etc.)

The serious pediatric NP cases in the current review are qualitatively similar to those described in the 2007 OSE review (e.g., hallucinations, abnormal behavior, delirium, etc.) and to reported co-morbidities. It is noted that whereas prior to 2008, most serious NP AEs in pediatric patients originated from Japan, from 2008-2009 the number of US reports rose, as did reports from countries other than US and Japan. Thereafter, the number of NP AEs from all countries appeared to decrease. These findings may be related to a combination of the following: NP labeling changes in the US label implemented in February 2008, increased US drug use during the 2009 H1N1 influenza pandemic, intrinsic pathogenicity of the 2009 H1N1 influenza virus and its presence in the US, or other unidentified factors.

In this review, most deaths were attributable to complications of influenza (e.g., pneumonia, encephalopathy, myocarditis), or co-morbidities (e.g., tuberculosis, failure of cardiac shunt). This review also describes deaths that were reported as, or coded in AERS with the MedDRA term, 'sudden death'. Pathology findings reported in the one patient with 'sudden death' who was autopsied noted a markedly congested and swollen brain and influenza induced cerebral disease. In 3 of the sudden death cases, clinical diagnoses of myocarditis were reported. Since influenza itself can cause myocarditis, and based on limitations of AERS data such as lack of control for co-morbidities, it is difficult to determine if these cases were causally related to oseltamivir or disease. Results from a QT study conducted in 2000 appeared to indicate that oseltamivir does not prolong QT intervals at therapeutic and supratherapeutic doses; however the study lacked a positive control.

No unexpected serious AEs related to oseltamivir were noted in a review of the subset of infant cases (≤12 months old). There were reports of nervous system disorders, such as seizures, and gastrointestinal related events; however, they are labeled events and were not unlike those seen in older populations.

5 CONCLUSIONS

Based on this review of AERS data, no new safety signals were identified in pediatric patients (0 to 16 years of age) exposed to oseltamivir. The majority of fatalities reported to AERS with oseltamivir use appear to be related to influenza disease progression. From 2008 to 2009 the number of US NP AE reports increased as did reports from other foreign countries. Additionally, during the 2009 H1N1 pandemic, worldwide reports of NP AEs increased. Thereafter, NP AE reports from all countries decreased.

6 RECOMMENDATIONS

DPV recommends continuing routine pharmacovigilance. Additionally, given the changing trend in reporting for neuropsychiatric AEs, DPV recommends that consideration be given to removing the text 'mostly from Japan' from the description of neuropsychiatric AEs in the Warnings and Precautions section of the Tamiflu label.

7 REFERENCES

1. Lewis L, Laessig K. FDA Medical Officer Supplemental Labeling Review, NDAs 21-087 and 21-246, June 2004.

2. Jones, SC. A Summary of all AERS Adverse Events reported in Infants ≤ 12 months following the administration of oseltamivir. May 2009.

3. Rothstein A, Edwards E, Truffa M. Tamiflu (oseltamivir) – Safety Update on Neuropsychiatric Events: Review of Neuropsychiatric Events with other antiviral products. November 2007.

4. Tamiflu Labeling: Revised March 2011.

8 APPENDICES

8.1 APPENDIX A: PEDIATRIC PRODUCT LABELING

The recommended oral dose of TAMIFLU for pediatric patients 1 year and older following close contact with an infected individual is shown in Table 1. For pediatric patients who cannot swallow capsules, TAMIFLU for oral suspension is the preferred formulation. If the oral suspension product is not available, TAMIFLU capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup, corn syrup, caramel topping, or light brown sugar (dissolved in water). If the appropriate strengths of TAMIFLU capsules are not available to mix with sweetened liquids and the oral suspension product is not available, then a pharmacist may compound an emergency supply of oral suspension from TAMIFLU 75 mg capsules *[see Dosage and Administration (2.8)]*.

Prophylaxis in pediatric patients following close contact with an infected individual is recommended for 10 days. Therapy should begin within 2 days of exposure. For prophylaxis in pediatric patients during a community outbreak of influenza, dosing may be continued for up to 6 weeks.

2.1 Dosing for Treatment and Prophylaxis of Influenza

TAMIFLU may be taken with or without food *[see Clinical Pharmacology (12.3)]*. However, when taken with food, tolerability may be enhanced in some patients.

The recommended oral treatment and prophylaxis dose of TAMIFLU for patients 1 year of age and older is shown in Table below directly from the Tamiflu labeling revised March 2011.

Treatment and Prophylaxis Dosing of Oral TAMIFLU for Influenza

For Patients 1 Year of Age and Older Based on Body Weight **Weight (kg)**	**Weight (lbs)**	**Treatment Dosing for 5 days**	**Prophylaxis Dosing for 10 days**	**Volume of Oral Suspension (6 mg/mL) for each Dose***	**Number of Bottles of Oral Suspension to Dispense**	**Number of Capsules and Strength to Dispense**
15 kg or less	33 lbs or less	30 mg **twice** daily	30 mg **once** daily	5 mL	1 bottle	10 Capsules 30 mg
16 kg thru 23 kg	34 lbs thru 51 lbs	45 mg **twice** daily	45 mg **once** daily	7.5 mL	2 bottles	10 Capsules 45 mg
24 kg thru 40 kg	52 lbs thru 88 lbs	60 mg **twice** daily	60 mg **once** daily	10 mL	2 bottles	20 Capsules 30 mg
41 kg or more	89 lbs or more	75 mg **twice** daily	75 mg **once** daily	12.5 mL†	3 bottles	10 Capsules 75 mg

Pediatric Patients TAMIFLU is not indicated for treatment of influenza in pediatric patients younger than 1 year.

The recommended oral dose of TAMIFLU for pediatric patients 1 year and older is shown in Table 1. For pediatric patients who cannot swallow capsules, TAMIFLU for oral suspension is the preferred formulation. If the oral suspension product is not available, TAMIFLU capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup, corn syrup, caramel topping, or light brown sugar (dissolved in water). If the appropriate strengths of TAMIFLU capsules are not available to mix with sweetened liquids and the oral suspension product is not available, then a pharmacist may compound an emergency supply of oral suspension from TAMIFLU 75 mg capsules *[see Dosage and Administration (2.8)]*.

Pediatric Patients The safety and efficacy of TAMIFLU for prophylaxis of influenza in pediatric patients younger than 1 year of age have not been established.

The recommended oral dose of TAMIFLU for pediatric patients 1 year and older following close contact with an infected individual is shown in Table 1. For pediatric patients who cannot swallow capsules, TAMIFLU for oral suspension is the preferred formulation. If the oral suspension product is not available, TAMIFLU capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup, corn syrup, caramel topping, or light brown sugar (dissolved in water). If the appropriate strengths of TAMIFLU capsules are not available to mix with sweetened liquids and the oral suspension product is not available, then a pharmacist may compound an emergency supply of oral suspension from TAMIFLU 75 mg capsules *[see Dosage and Administration (2.8)]*.

Prophylaxis in pediatric patients following close contact with an infected individual is recommended for 10 days. Therapy should begin within 2 days of exposure. For prophylaxis in pediatric patients during a community outbreak of influenza, dosing may be continued for up to 6 weeks.

Treatment Studies in Pediatric Subjects A total of 1032 pediatric subjects aged 1 to 12 years (including 698 otherwise healthy pediatric subjects aged 1 to 12 years and 334 asthmatic pediatric subjects aged 6 to 12 years) participated in controlled clinical trials of TAMIFLU given for the treatment of influenza. A total of 515 pediatric subjects received treatment with TAMIFLU for oral suspension.

Adverse events occurring in ≥1% of pediatric subjects receiving TAMIFLU treatment are listed in Table 5. The most frequently reported adverse event was vomiting. Other events reported more frequently by pediatric 247 subjects treated with TAMIFLU included abdominal pain, epistaxis, ear disorder, and conjunctivitis. These events generally occurred once and resolved despite continued dosing resulting in discontinuation of drug in 8 249 out of 515 (2%) cases. The adverse event profile in adolescents is similar to that described for adult subjects and pediatric subjects 251 aged 1 to 12 years.

8.4 Pediatric Use The safety and efficacy of TAMIFLU in pediatric patients younger than 1 year of age have not been studied. TAMIFLU is not indicated for either treatment or prophylaxis of influenza in pediatric patients younger than 1 year of age because of the unknown clinical significance of nonclinical animal toxicology data for human infants *[see Nonclinical Toxicology (13.2)]*.

8.2 APPENDIX B: STANDARD SEARCHES

A. Adults (17 yrs and above)
   1. All outcomes from approval date (no set criteria)
   2. Serious outcomes from approval date
   3. Death as an outcome from approval date

B. Ages 0-16 yrs ONLY
   1. Same as above 1-3

MedDRA Search Terms used to identify Neuropsychiatric Events with Oseltamivir in AERS

ABNORMAL BEHAVIOUR NEC (HLT) ABNORMAL SLEEP-RELATED EVENTS (HLT) ABSENCE SEIZURES (HLT) ACCIDENT (PT) ACCIDENT AT HOME (PT) AFFECT ALTERATIONS NEC (HLT) ANXIETY DISORDERS NEC (HLT) ANXIETY SYMPTOMS (HLT) ATTENTION DEFICIT AND DISRUPTIVE BEHAVIOUR DISORDERS (HLT) BEHAVIOUR AND SOCIALISATION DISTURBANCES (HLT) CENTRAL NERVOUS SYSTEM VASCULAR DISORDERS NEC (HLT) COMA STATES (HLT) COMMUNICATIONS DISORDERS (HLT) CONFUSION AND DISORIENTATION (HLT) CORTICAL DYSFUNCTION NEC (HLT) DELIRIA (HLT) DELUSIONAL SYMPTOMS (HLT) DISTURBANCES IN CONSCIOUSNESS NEC (HLT) DISTURBANCES IN INITIATING AND MAINTAINING SLEEP (HLT) DYSSOMNIAS (HLT) EMOTIONAL AND MOOD DISTURBANCES NEC (HLT) ENCEPHALITIS NEC (HLT) ENCEPHALITIS OF VIRAL ORIGIN (HLT) ENCEPHALOPATHIES NEC (HLT) ENCEPHALOPATHIES TOXIC AND METABOLIC (HLT) FALL (PT) FEAR SYMPTOMS AND PHOBIC DISORDERS (INCL SOCIAL PHOBIA) (HLT) FRACTURES AND DISLOCATIONS NEC (HLT) GENERALISED TONIC-CLONIC SEIZURES (HLT)	IMPULSE CONTROL DISORDERS (HLT) INCREASED PHYSICAL ACTIVITY LEVELS (HLT) INJURY (PT) INTENTIONAL SELF-INJURY (PT) MEMORY LOSS (EXCL DEMENTIA) (HLT) MENTAL IMPAIRMENT (EXCL DEMENTIA AND MEMORY LOSS) (HLT) MOOD ALTERATIONS WITH DEPRESSIVE SYMPTOMS (HLT) MOOD DISORDERS NEC (HLT) NEUROLOGIC VISUAL PROBLEMS NEC (HLT) PANIC ATTACKS AND DISORDERS (HLT) PARALYSIS AND PARESIS (EXCL CRANIAL NERVE) (HLT) PARASOMNIAS (HLT) PARTIAL COMPLEX SEIZURES (HLT) PERCEPTION DISTURBANCES (HLT) PERSONALITY DISORDERS NEC (HLT) PSYCHIATRIC SYMPTOMS NEC (HLT) ROAD TRAFFIC ACCIDENT (PT) SEIZURES AND SEIZURE DISORDERS NEC (HLT) SLEEP DISORDERS DUE TO GENERAL MEDICAL CONDITION (HLT) SLEEP DISORDERS NEC (HLT) SPECIFIC COGNITIVE ABILITY DISTURBANCES (HLT) SPEECH AND LANGUAGE ABNORMALITIES (HLT) SPEECH AND LANGUAGE USAGE DISTURBANCES (HLT) STRUCTURAL BRAIN DISORDERS NEC (HLT) SUICIDAL AND SELF-INJURIOUS BEHAVIOUR (HLT) THINKING DISTURBANCES (HLT) TRAUMATIC CENTRAL NERVOUS SYSTEM HAEMORRHAGES (HLT)

8.3 APPENDIX C: DATA MINING RESULTS

Table C1: Data Mining Results Stratified by Age			
Preferred Term (PT)	**Age Subset**	**N**	**EB05**
Caesarean section	00-01	29	2.536
Hallucination	00-01	6	2.73
Incorrect dose administered	00-01	10	2.432
No adverse event	00-01	32	10.508
Normal newborn	00-01	35	9.656
Pathogen resistance	00-01	6	8.227
Abnormal behaviour	02-05	80	3.875
Delirium	02-05	23	8.876
Hallucination	02-05	32	3.266
Hypothermia	02-05	14	4.36
No adverse event	02-05	36	2.309
Pathogen resistance	02-05	9	5.332
Sudden death	02-05	9	3.288
Abnormal behaviour	06-11	161	4.342
Confusional state	06-11	23	2.202
Delirium	06-11	53	7.527
Delirium febrile	06-11	6	2.444
Hallucination	06-11	82	4.837
Hallucination, auditory	06-11	15	2.168
Hypothermia	06-11	10	2.417
Nightmare	06-11	20	2.148
No adverse event	06-11	21	2.285
Sleep terror	06-11	10	2.167
Abnormal behaviour	12-16	100	6.309
Confusional state	12-16	21	2.829
Delirium	12-16	22	5.138
Delusion	12-16	10	3.518
Depressed level of consciousness	12-16	17	2.538
Hallucination	12-16	42	4.613

8.4 APPENDIX D: DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor AEs and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. AEs in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Data Mining of AERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the Adverse Event Reporting System (AERS) database is utilized for data mining. MGPS analyzes the records in AERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in AERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Elevated EB05 values are used to detect potential safety issues only. Elevated EB05 values do not imply pathophysiological relationship or causality between the drug and event of interest. Because EBGM scores are based on AERS data, limitations relating to AERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.5 APPENDIX E: AERS CRUDE DATA: FDA RECEIVE DATE JUNE 1, 2007 THROUGH DECEMBER 31, 2011 WITH A FOCUS ON SERIOUS PEDIATRIC REPORTS (0 TO 16 YEARS) WITH OSELTAMIVIR

Table E1: AERS Crude Data (combined HLTs and PTs listed in Appendix B): June 1, 2007 through December 31, 2011 with a focus on Serious Pediatric Reports (0 to 16 years) with Oseltamivir

	2007*			2008			2009			2010			2011			
	Total	US	JP	Total	US	JP	Total	US	JP	Total	US	JP	Total	US	JP	**Totals**
Total Pediatric Reports N (%)	103 (53)§	6 (6)	91 (88)	169 (49)§	76 (46)	87 (50)	376 (33)§	105 (30)	80 (23)	153 (23)§	25 (17)	56 (37)	101 (25)§	27 (32)	26 (28)	902
Total Reports- All ages	*194*	*16 (8)*	*165 (85)*	*343*	*159 (46)*	*147 (43)*	*1145*	*243 (21)*	*225 (20)*	*657*	*85 (13)*	*201 (30)*	*397*	*87 (22)*	*86 (22)*	***2736***
Total Pediatric NP reports N (%)	91	4 (4)	83 (91)	140	57 (41)	79 (56)	255	63 (25)	67 (26)	66	11 (17)	30 (45)	48	17 (35)	18 (37)	**600**
Pediatric NP events/ Total Pediatric Reports (%)	*88*	*4*	*80*	*83*	*34*	*47*	*68*	*17*	*18*	*43*	*7*	*20*	*47*	*17*	*18*	
All Cause Pediatric Death N (%)	5	0 (0)	5 (100)	6	1 (20)	4 (60)	43	1 (53)	17 (42)	35	4 (11)	10 (32)	26	4 (10)	1 (5)	**115**
Total US Pediatric Deaths Attributed to NP Events		0			0			0			0			**0**		

NP=Neuropsychiatric reports; * 2007 [June 1, 2007 through December 31, 2011]; § Percent of pediatric cases compared to all ages

8.6 APPENDIX F: LINE LISTING OF CASES

Table F1. Adverse Events reported with Tamiflu in Patients ≤ 12 months old with FDA Receive Date from June 1, 2007 through December 31, 2011.

ISR #/Case #	FDA Receive date/ Event Date	Age	SEX	Country	Outcome*	Weight (kg)	Daily dose	Duration of therapy (days) Reported Preferred Terms	Case Notes
5423869 6320394	23-Aug-07 18-Feb-07	10 month	Male	JP	OT	9 kg	75mg PO BID	3 days liver disorder	Patient was prescribed oseltamivir 75 mg PO BID. On day 2 of hospital admission, patient's LFTs increased and oseltamivir was discontinued. Healthy twin brother also showed increased LFTs to oseltamivir.
5675132 6560535	20-Mar-08 2-Feb-08	1 year	Male	JP	OT	9 kg	not reported	4 days abnormal behaviour,	After taking the first dose, the patient acted violently and became out of control. The second dose could not be administered on this date. On 5 Feb 2008, oseltamivir was discontinued. On an unspecified date, "abnormal behaviour" resolved. The reporter considered that the event was not an adverse reaction of oseltamivir, but was caused by high fever due to influenza.
5796603 6279584	1-Jul-08 1-Jan-03	10 month	Female	JP	LT	not reported	18mg PO BID	1 day	Three days after testing negative for influenza, patient revisited the hospital and was prescribed oseltamivir 18mg PO BID. About 50 minutes after taking the dose, the patient fell down with flaccid extremities and lost consciousness with cyanotic lips and froth. She required treatment with diazepam for a life threatening clonic convulsion and she regained consciousness 1.5 hours later. Pyrexia resolved after 5 days from onset. She was suspected of having muscular disease when she was seen at 17 months old. Reporter's Comment: it may be the central suppressing effect of oseltamivir that caused respiratory depression, hypoxemia, and hypoxic encephalopathy, which resulted in convulsion and delayed nerve cell disorder following systemic ischemia (cardio-

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ISR #/Case #	**FDA Receive date/ Event Date**	**Age**	**SEX**	**Country**	**Outcome***	**Weight (kg)**	**Daily dose**	**Duration of therapy (days)** **Reported Preferred Terms**	**Case Notes**
								cardio-respiratory arrest, respiratory depression, hypoxia, convulsion, fall, hypoxic-ischaemic encephalopathy, cyanosis, hypotonia, developmental delay, loss of consciousness	respiratory arrest)
5817643 6612948	22-Jul-08 9-Feb-06	8 months	Female	JP	OT	8 kg	not reported	4 days abnormal behaviour	Patient had a confirmed diagnosis of influenza and was started on oseltamivir. One and 1/2 hours after taking oseltamivir, patient developed abnormal behavior of banging head on mother's breast. Abnormal behavior did not continue despite continuing oseltamivir.
6192054 6995888	15-May-09 not reported	1 year	Unk	US	DE	not reported	not reported	not reported pathogen resistance	This patient was admitted to hospital in respiratory failure. The patient was deemed do not resuscitate, and died due to oseltamivir resistant influenza. The authors stated that this patient had multiple severe underlying medical conditions (unspecified) which put him/her at high risk for complications associated with influenza virus infection.
6258256 7047865	2-Jul-09 28-Jun-09	4 months	Female	US	OT	8.2 kg	20 mg PO BID	4 days convulsion	Seizures witnessed by parents on days 3 and 4 of oseltamivir therapy. Oseltamivir was discontinued and seizures resolved.
6305412 7078646	11-Aug-09 not reported	11 month	Male	GB	OT	not reported	not reported	not reported convulsion	an 11 month old male patient who experienced seizure while treated with oseltamivir for an unreported indication. The patient's medical history was not provided. No concomitant or past drugs were reported. On an unspecified date the patient started oseltamivir and subsequently experienced a seizure. The seizure had a final outcome of recovered. There

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ISR #/Case #	**FDA Receive date/ Event Date**	**Age**	**SEX**	**Country**	**Outcome***	**Weight (kg)**	**Daily dose**	**Duration of therapy (days)** **Reported Preferred Terms**	**Case Notes**
									was insufficient information to determine the action taken with oseltamivir.
6317530 7087325	21-Aug-09 28-Jul-09	1 year old	Male	GB	OT	not reported	not reported	not reported diarrhoea, rash generalised, abdominal pain, flatulence, headache, hallucination, vomiting	A 1 year old male patient who experienced the events of hallucinating, vomiting, diarrhea, malodorous flatulence, headache, rash all over and abdominal pain while treated with oseltamivir (tamiflu) for an unknown indication. The patient's concomitant medication included paracetamol and ibuprofen. On 28 july 2009, the patient started with oseltamivir 30 mg twice daily (route and form were unspecified). On the same day, the patient experienced hallucinating, vomiting, diarrhea, malodorous flatulence, headache, rash all over. On 29 July 2009, the patient experienced abdominal pain. On 01 August 2009, therapy of oseltamivir was discontinued. On the same day, the event rash all over was improved. On 02 august 2009, the event vomiting was resolved. On 03 august 2009, the event hallucinating was improved. On 04 august 2009, the event malodorous flatulence was improved and the event headache was resolved. Outcome of the event abdominal pain was improved and the event diarrhoea was persisting.
6326830 7095497	25-Aug-09 not reported	7 month	Female	IN	DE	not reported	not reported	not reported acute respiratory distress sydrome, pneumonia viral	a 7 month old female patient who experienced adult respiratory distress syndrome and viral bronchopneumonia while treated with oseltamivir (Tamiflu) for H1N1 influenza. No concurrent conditions and relevant medical history was reported. No concomitant or past drugs were reported. On (b) (6), the patient was admitted to a private hospital for meningitis and excessive sleep syndrome. On the same day, her throat swabs were sent for testing as she displayed symptoms of the flu. She was tested positive for swine flu on (b) (6). On an unknown day, the patient started oseltamivir (dose, route, form, frequency: unknown). She was shifted to the intensive care unit and put on ventilator as she had stopped responding to medical treatment. On an unknown day, the patient experienced the event of fatal adult respiratory distress syndrome and fatal viral bronchopneumonia.

Table F1. Adverse Events reported with Tamiflu in Patients ≤ 12 months old with FDA Receive Date from June 1, 2007 through December 31, 2011.

ISR #/Case #	FDA Receive date/ Event Date	Age	SEX	Country	Outcome*	Weight (kg)	Daily dose	Duration of therapy (days) Reported Preferred Terms	Case Notes
6383456 7135942	1-Oct-09 25-Aug-09	9 month	Female	GB	OT	not reported	not reported	5 days somnolence, convulsion	Patient finished a 5 day course of oseltamivir. The next day, the patient experienced afebrile seizure with a stiff distorted face and stiff body, gazed eyes and was not responsive for a minute. No causality assessment was provided.
6383672 7153270	29-Sep-09 25-Sep-09	1 year	Male	US	OT	9.5 kg	2.5 ml PO BID [unknown concentration]	not reported middle insomnia, screaming, rash, vomiting, abdominal pain upper	My son vomited 3 times after taking Tamiflu. He had bad stomach cramps and fell right to sleep about an hour after medication from feeling so bad. He woke up first night screaming in the middle of night and would not go to bed. He got a rash after taking 6 doses or on the third day. I have stopped the medication.
6401268 7151821	9-Oct-09 24-Sep-09	25 days	Female	US	HO	2 kg	12 mg x 1	1 day apnoea, grand mal convulsion	Patient had signs/symptoms of possible sepsis, starting the day before he was initiated on oseltamivir. Four hours after receiving the dose, he had a generalized tonic-clonic seizure lasting 4 minutes and requiring a bag/mask ventilation for apnea. Seizure resolved spontaneously without anticonvulsant therapy.
6401285 7165496	9-Oct-09 8-Oct-09	3 month	Female	US	OT	5.66 kg	20 mg PO BID	4 days diarrhoea, haematochezia	Three month old developed diarrhea and blood streaked stools. Resolved without problems. Patient developed influenza while hospitalized.
6408204 7154050	21-Oct-09 23-Sep-09	6 months	Male	HK	HO	not reported	2.5 ml PO BID [unknown Concentration]	not reported tongue ulceration, infection, neutropenia	The patient experienced progression of a preexisting tongue ulcer, neutropenia and infection while on oseltamivir. On (b) (6) [redacted], a big and deep ulcer around 1 cm over the anterior part of surface of the tongue with overlying scabbing and surrounding erythema was noticed . On the same date, the baby was admitted to hospital for the management where neutropenia was identified and chest-x ray showed bronchitic changes. The reporter assessed the causality between the events of progression of pre-existing tongue ulcer, neutropenia and infection to oseltamivir as unknown.
6419177 7164862	28-Oct-09 27-Oct-09	6 months	Male	US	OT	6.2 kg	not reported	not reported screaming	Mother reports her 6 month old son was screaming for 3 hours after taking oseltamivir the night before.

Table F1. Adverse Events reported with Tamiflu in Patients ≤ 12 months old with FDA Receive Date from June 1, 2007 through December 31, 2011.

ISR #/Case #	FDA Receive date/ Event Date	Age	SEX	Country	Outcome*	Weight (kg)	Daily dose	Duration of therapy (days) / Reported Preferred Terms	Case Notes
6435078 7186818	9-Nov-09 2-Nov-09	4 months	Male	US	OT	8.2 kg	105 mg PO BID	2 days vomiting, disturbance in attention, somnolence, diarrhoea, lethargy, medication error, overdose	Consumer reported that her son received an overdose of oseltamivir. On the second day of this medication, the patient had multiple diarrhea and vomiting. He was very sleepy and had a hard time focusing. The prescribed dose was to be 20mg PO BID.
6436219 7173732	11-Nov-09 not reported	1 year	Unk	JP	OT	not reported	not reported	not reported abnormal behaviour	Concerns a 1-year-old and sex unspecified patient with influenza, who experienced abnormal behaviour, while/after receiving oral oseltamivir (Tamiflu) for the treatment of influenza. Clinical course: an unspecified date oseltamivir (Tamiflu) was started for influenza. An unspecified date the patient experienced abnormal behavior with running around the bed after having taken oseltamivir for 3 days.
6439600 7176511	13-Nov-09 28-Sep-09	7.5 months	Male	FR	HO	not reported	25mg PO BID	1.5 days diarrhoea haemorrhagic, diarrhoea	On [redacted] (b) (6), i.e. 36 hours after amoxicillin trihydrate + potassiumclavulanate and oseltamivir start, the patient experienced bloody diarrhea. Treatment with amoxicillin trihydrate + potassium clavulanate and oseltamivir was discontinued. Search for rotavirus and clostridium difficile was negative .The patient was switched to ceftriaxone (Rocephine) and treated with metronidazole (Flagyl). The events resolved within 48 hours: normal stools and good general health status were reported. The patient was hospitalised for four days and was discharged with metronidazole. The AFSSaPS assessed the causal relationship of amoxicillin trihydrate +potassium clavulanate and/or oseltamivir with the events as possible, according to the French method of assessment.
6444536 7182547	17-Nov-09 10-Nov-09	4 months	Male	US	OT	6.74 kg	18mg PO BID	1 day seborrhoeic dermatitis, rash macular	10 hours after taking the first and only dose of oseltamivir, patient developed a diffuse rash with discrete macules and it was located on forehead, chest, back and legs. Rash was not itchy. Patient was also noted to have seborrheic dermatitis of the scalp.

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ISR #/Case #	**FDA Receive date/ Event Date**	**Age**	**SEX**	**Country**	**Outcome***	**Weight (kg)**	**Daily dose**	**Duration of therapy (days)** **Reported Preferred Terms**	**Case Notes**
6446266 7170302	19-Nov-09 27-Oct-09	2 months	Female	CA	OT	not reported	60mg PO BID	1.5 days no adverse event, accidental overdose	Patient accidently received an overdose of oseltamivir [was supposed to receive 12mg PO BID]. No adverse events noted.
6452689 7220554	23-Nov-09 10-Nov-09	2.5 months	Male	US	HO	7.95 kg	1 ml BID [unknown concentration]	7 days dyskinesia, cyanosis, partial seizures	New onset seizures which required hospitalization for partial seizures. Abnormal EEG with unilateral frontocentra focus, becoming bilateral on repeat. Seizures are controlled with Keppra.
6458771 7190834	27-Nov-09 15-Nov-09	48 weeks	Female	NL	OT	not reported	30 mg PO BID	2 days restlessness, hallucination, sleep disorder, anxiety	48 week old who experienced anxiety, restlessness, sleeping problems, and hallucination like symptoms while on oseltamivir. She was started on oseltamivir 30mg PO BID and that same day developed neuropsych AE s including difficultly falling asleep, waking up screaming. Oseltamivir was discontinued after 3 doses. The reporter consider the events to be related to oseltamivir.
6483562 7213909	8-Dec-09 18-Nov-09	9 months	Male	US	OT	9.5 kg	30 mg PO BID	2 days dyskinesia, hallucination, poisoning, unevaluable event, strabismus, vomiting, abnormal behaviour	Parent states patient acted as if he had hallucinations after first dose of oseltamivir. Upon second dose, he was acting as if he was intoxicated. The provider instructed the parent not to give oseltamivir anymore. Neurologist did not find anything wrong on EEG.
6486694 7209831	10-Dec-09 1-Jan-09	1 year	Male	JP	DE	not reported	not reported	Not reported	1 YO patient who was diagnosed with influenza. CT scan showed mild cerebral atrophy, patient was intubated, admitted to ICU. When transferred to general wards developed renal

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ISR #/Case #	FDA Receive date/ Event Date	Age	SEX	Country	Outcome*	Weight (kg)	Daily dose	Duration of therapy (days) / Reported Preferred Terms	Case Notes
								Cardiac failure, renal failure, encephalopathy	failure and cardiac failure. He died 20 days after transfer to general wards due to acute necrotic encephalopathy and renal/cardiac failure. No drug-event causality reported.
6517228 7289304	17-Dec-09 1-Apr-08	1 year	Male	US	OT	not reported	not reported	not reported / psychotic disorder	Limited information: ' It was like he was psychotic.'
6517231 7289343	17-Dec-09 not reported	2 weeks	Unk	US	HO	not reported	not reported	1 day / bilirubin conjugated increased	Patient's bilirubin increased and patient required hospitalization. The patient received only two doses of oseltamivir.
6534018 7242878	12-Jan-10 31-Dec-09	1 year	Male	JP	DE	not reported	not reported	not reported / encephalopathy	Cause of death influenza encephalopathy (caused by influenza a/h1n1 virus infection) patient background a 1-year-old male patient
6549071 7254495	25-Jan-10 not reported	6 months	Male	GB	OT	not reported	not reported	2 days / hypoglycaemia	On an unspecified date, the patient started taking oseltamivir. He subsequently experienced hypoglycemia. FDA reviewer: Drug event causality is difficult to determine.
6596413 7290437	23-Feb-10 not reported	1 year	Male	HK	DE	not reported	not reported	not reported / drug ineffective	A one year old boy who experienced fatal lack of efficacy while receiving oseltamivir for human swine influenza. On 01 December 2009, the patient developed flu symptoms with congenital heart disease and attended the accident and emergency departmen on (b) (6). He was admitted to pediatric general ward and later admitted to

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ISR #/Case #	FDA Receive date/ Event Date	Age	SEX	Country	Outcome*	Weight (kg)	Daily dose	Duration of therapy (days) Reported Preferred Terms	Case Notes
									pediatric intensive care unit on [redacted] (b) (6), positive result of hsi was confirmed. The patient was prescribed with oseltamivir and antibiotics and was on ventilation support. The patient was transferred to the pediatric intensive care unit, [redacted] (b) (6) for further treatment for his underlying diseases on [redacted] (b) (6). His condition further deteriorated due to lack of effect and he finally succumbed on [redacted] (b) (6)
6731441 7396453	18-May-10 20-Oct-09	2 months	Male	US	HO	8 kg	not reported	1 day depressed level of consciousness, decreased appetite, oxygen saturation decreased	Limited information: Desaturations into the upper 70s multiple times, loss of appetite, and decreased level of consciousness.
6736131 7396023	21-May-10 9-Nov-09	2 weeks	Male	FR	HO	3.4 kg	10 mg PO BID	5 days frequent bowel movements, weight decreased, jaundice	5 days after starting oseltamivir, patient experienced weight loss > 12% and diarrhea [more than 10 stools/daily. He also presented with jaundice and was hospitalized.
6801472 7441261	29-Jun-10 not reported	1 year	Male	IN	DE	not reported	not reported	not reported death	Concerns a 01 year old male patient who experienced death while treated with oseltamivir (Tamiflu) for h1n1 influenza. No concurrent conditions or medical history was reported. No concomitant medications or past drugs were reported. On 12 June 2010, the patient was suffering from fever. On [redacted] (b) (6), the patient was hospitalized on developing breathlessness. The patient was suspected that he was suffering from swine flu and his throat swabs were taken. On an unspecified date, the patient started the therapy with oseltamivir for three days (route, form, frequency and dose: not mentioned) after testing h1 n1 positive. On [redacted] (b) (6), the patient developed complications and was admitted to pediatric ICU and on the same day the patient died.

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ISR #/Case #	**FDA Receive date/ Event Date**	**Age**	**SEX**	**Country**	**Outcome***	**Weight (kg)**	**Daily dose**	**Duration of therapy (days)** **Reported Preferred Terms**	**Case Notes**
6876844 7503106	27-Jul-10 not reported	11 months	Male	IN	DE	not reported	not reported	1 day H1N1 influenza	The patient was started on oseltamivir and died the same day. He had a medical history of kidney disorder and was on corticosteroids for this kidney disorder. No drug event causality was noted.

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ISR #/Case #	FDA Receive date/ Event Date	Age	SEX	Country	Outcome*	Weight (kg)	Daily dose	Duration of therapy (days) / Reported Preferred Terms	Case Notes
7009834 7603150	23-Sep-10 not reported	1 year	Female	AR	OT	10.6 kg	30mg PO BID	4 + 8 [2 courses] / lung disorder, drug ineffective, pathogen resistance	On (b) (6), a previously healthy 1 year old girl weighing 10.6kg was hospitalized for pneumonia and empyema. Five days before admission, she presented with fever and progressive respiratory symptoms. On admission to the ICU, she was hypoxic and febrile, with consolidation in the upper right pulmonary lobe, and required mechanical ventilation. Streptococcus pneumoniae bacteremia was detected. Although, tracheal aspiration (tracheal aspirate: ta) was negative for influenza virus, oseltamivir 30mg twice daily, with ceftriaxone, vancomycin, was administered for 4 days. Dexamethasone treatment (0.6mg/day) was added on (b) (6) and continued for 9days, replaced then by hydrocortisone (60mg/ day), which continued until discharge. On (b) (6), the lung disease worsened, and the culture of pleural drainage recovered klebsiella pneumoniae. At the same time, pandemic h1n1 2009 was detected in tracheal aspiration, thus oseltamivir treatment was restarted at a dose of 30 mg twice daily for 8days. In the following days, her condition worsened, with infiltrates involving the other lung. She also had haemodynamic compromise, requiring inotropics. Following right upper lobectomy because of bronchopleural fistula, she was discharged on (b) (6). There was insufficient information regarding the outcome of the event of oseltamivir resistant pandemic (h1n1) 2009 and lung disease worsened.

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ISR #/Case #	FDA Receive date/ Event Date	Age	SEX	Country	Outcome*	Weight (kg)	Daily dose	Duration of therapy (days) Reported Preferred Terms	Case Notes
7126102 7685191	29-Nov-10 not reported	6 months	Male	ES	HO	7 kg	12 mg PO BID	15 days neurotoxicity, drug resistance, respiratory failure, graft versus host disease, pathogen resistance	On day 10, patient presented with fever and respiratory insufficiency requiring oxygen therapy. On day 12, patient developed grade ii acute gvhd which was treated with corticosteroids and tacrolimus. On day 19, respiratory difficulty persisted and a bronchoalveolar lavage (bal) was positive for influenza a (h3n2). On day 26 post-transplant, after 33 days of antiviral therapy, treatment was discontinued and the patient was discharged from hospital with the influenza a infection apparently resolved. On day 38, fever, rash and upper respiratory symptoms reappeared. Tlc was 1577 cells/mm3. A nasal antigen detection swab showed that the influenza a infection remained unresolved. The patient was again started on oseltamivir 12 mg once daily and amantadine 7.5 mg once daily for 15 days. The patient developed neurological toxicity due to which the dose of amantadine was reduced to 7.5 mg once daily. The authors discussed that the e119v mutation detected in the immunocompromised infant with prolonged shedding confers oseltamivir resistance. They also discussed that the prolonged subtherapeutic dose of both anti-virals might have contributed to the development of resistance and the lack of viral clearance. The authors also expressed the possibility that the patient was infected with an already amantadine or oseltamivir resistant virus. The company assessed the events of oseltamivir resistance, amantadine resistance, neurological toxicity, and grade ii and iii GVHD (graft versus host disease) as medically significant.

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ISR #/Case #	**FDA Receive date/ Event Date**	**Age**	**SEX**	**Country**	**Outcome***	**Weight (kg)**	**Daily dose**	**Duration of therapy (days)** **Reported Preferred Terms**	**Case Notes**
7287125 7803852	11-Feb-11 not reported	1 year	Unk	JP	OT	not reported	not reported	not reported abnormal behaviour, gait disturbance	Pharmacist and concerns a 01 year old patient of unknown sex who experienced abnormal behavior while treated with oseltamivir (Tamiflu) for an unreportable indication. No concurrent conditions and relevant medical history was reported. No concomitant or past drugs were reported. On an unknown date, the patient started oral oseltamivir capsule (dosage was uncertain and frequency: not reported). It was reported that, the patient started to walk at age of 1.1 year. It was reported that, after several months later, the patient's way of walking was different bumping against the wall after oseltamivir was given, of which information was obtained by his/her mother. There was insufficient information regarding the outcome of the event of abnormal behavior.
7303790 7820188	21-Feb-11 28-Jan-11	2 months	Male	TW	DE	not reported	not reported	not reported H1N1 Influenza	Two month old who died of H1N1 influenza while on treatment for H1N1 influenza with oseltamivir. Patient required ICU admission and died on (b) (6) of H1N1 influenza. The reporter assessed the cause of death as unrelated to oseltamivir. Patient with premature birth with gestational age of 30 weeks and birth weight of 1.7kg.
7303944 7820276	21-Feb-11 not reported	1 year	Unk	US	OT	not reported	not reported	not reported incorrect dose administered	Patient received 120mg vs 20mg dose. No other information given.
7496458 7231105	23-May-11 not reported	1 year	Female	KR	DE	not reported	not reported	6 days acute respiratory distress syndrome, pathogen resistance, drug ineffective, pneumonia	Patient died. Was found to have oseltamivir resistant influenza. She was co-infected with pneumonia and ARDS.
7618300	18-Jul-11	1 year	Femal	ES	DE	not	not reported	not reported	A one year old female patient (patient number: 1) who died

Table F1. Adverse Events reported with Tamiflu in Patients ≤ 12 months old with FDA Receive Date from June 1, 2007 through December 31, 2011.									
ISR #/Case #	**FDA Receive date/ Event Date**	**Age**	**SEX**	**Country**	**Outcome***	**Weight (kg)**	**Daily dose**	**Duration of therapy (days)** / **Reported Preferred Terms**	**Case Notes**
7978312	not reported		e			reported		pathogen resistance, drug ineffective	due to oseltamivir-resistant pandemic (h1n1) 2009 while being treated for influenza a (h1n1) virus. The patient was enrolled in a retrospective study. The aim of the study was to detect oseltamivir-resistant pandemic influenza a (h1n1) 2009 viruses by the spanish influeza
7762139 7771647	20-Sep-11 not reported	22 days	Unk	US	DE	not reported	not reported	10 days peritoneal haemorrhage, abdominal compartment syndrome	STUDY: This case concerns 1 of the 21 patients from the oseltamivir prophylaxis group. The patient had an underlying comorbidities of diaphragm eventration and bronchopulmonary sequestration, hemoperitoneum and abdominal compartment syndrome. On an unspecified date, the patient started receiving prophylaxis with 3.8 mg/kg of oseltamivir. The patient was receiving anticoagulation while on extracorporal membrane oxygenation. The patient died after 10 days of prophylaxis secondary to post-surgical complications with hemoperitoneum and abdominal compartment syndrome. The authors considered death due to hemoperitoneum and abdominal compartment syndrome to be unlikely related to oseltamivir.
7762159 7771685	20-Sep-11 not reported	47 days	Unk	US	DE	not reported	4.3mg/kg x 1	1 day hepatic failure, disseminated tuberculosis	STUDY: This case concerns 1 of the 21 patients from the oseltamivir prophylaxis group. The patient had an underlying comorbidity of miliary tuberculosis. On an unspecified date, the patient received 4.3 mg/kg of oseltamivir. After receiving this single dose, the patient experienced an increase in direct bilirubin (direct bilirubin: 7.9 mg/dl) without any changes in the transaminases. In view of the increased bilirubin, oseltamivir was stopped. Bilirubin continued to rise and 12 days after receiving oseltamivir, the infant succumbed to disseminated tuberculosis. The authors stated that the antiviral was intentionally stopped after the first dose in this patient with a rising bilirubin, however, disseminated tuberculosis shown at autopsy was more likely the cause of the patient's liver failure than the antiviral. The authors further stated that death was unlikely related to oseltamivir.
* Outcome: DE: Death, HO: Hospitalization, OT: Other, LT: Life Threatening									

Table F2: Line Listing of Pediatric (0 to 16) Death AERS Cases with FDA Receive Date from June 1, 2007 through December 15, 2011. (n=112)							
ISR #	**FDA Receive Date**	**Event Date (if known)**	**Calculated Age (years)**	**SEX**	**Country**	**reported preferred terms (PTs)**	**Case Summary**
5360646	18-Jun-07	31-Jan-06	8.6	Male	JP	shock haemorrhagic,	8 year old male with 2 day history of fever to 40C, diagnosed with influenza (type not reported). Started Tamiflu. Less than 24 hours later he was found pulseless/not breathing at home. CPR with brief documented pulse then died. Autopsy showed gastric ulcers with hemorrhage. Autopsy/histopath comment: chronic ulcers exacerbated by fever progressed to perforation. No direct relationship to oseltamivir.
5420917	21-Aug-07	3-Jul-06	12.8	Male	JP	pelvic fracture,injury,	12 YO male who was treated with oseltamivir and died from a hemorrhage 2/2 multiple fractures from a fall. Patient arrived at hospital in cardio-pulmonary arrest and died.
5520981	19-Nov-07	8-Mar-05	4.0	Female	JP	cardio-respiratory arrest,sudden death,	4 year old developed myocarditis and cardiopulmonary arrest with no response to resuscitation.
5520984*	19-Nov-07	30-Dec-02	2.5	Male	JP	cardiac arrest,sudden death,	2 YO who experienced cardiac arrest and experienced sudden death on day one of oseltamivir use. He required intubation and CPR/ACLS, but died. He had pseudocroup too.
5521007	19-Nov-07	16-Dec-05	7.1	Male	JP	cardio-respiratory arrest,gastrointestinal haemorrhage,sudden death,	Patient with cardio pulmonary arrest with failed resuscitation. Multiple organ failure could not be denied.
5714946*	23-Apr-08	21-Jan-08	12.0	Male	FR	status epilepticus,	12 YO without significant medical history presented with myoclonical status epilepticus seizure, then multiple organ failure with renal failure requiring HD, liver failure, DIC< septic shock with resistant bacteria. The main hypotheses were either post-infectious encephalitis or devastating epileptic encephalopathy in school age children. Patient died from multiple organ failure on day 24 after ICU admission.
5794968	30-Jun-08	16-Dec-02	3.0	Male	JP	blood glucose increased,respiratory arrest,sudden death,cardiac arrest,	3 YO M who experienced respiratory arrest and sudden death in sleep. Patient died suddenly in sleep.

Table F2: Line Listing of Pediatric (0 to 16) Death AERS Cases with FDA Receive Date from June 1, 2007 through December 15, 2011. (n=112)

ISR #	FDA Receive Date	Event Date (if known)	Calculated Age (years)	SEX	Country	reported preferred terms (PTs)	Case Summary
5800415	3-Jul-08	4-Feb-05	14.0	Male	JP	accidental death,abnormal behaviour,	14 YO who took oseltamivir 75mg and several hours later he climbed over the banister on their 9 story condo building and fell 9 stories to his death. He died of massive bleeding.
5821856	24-Jul-08	5-Feb-05	2.8	Male	JP	headache,cardio-respiratory arrest,body temperature decreased,	Literature article: 33 month old who died due to CPR during a nap after experiencing hypothermia while on oseltamivir for treatment of influenza. He died due to hyoxic organ failure. CPR thought to be due to oseltamivir use.
5907700	3-Oct-08	14-Mar-07	3.0	Male	JP	cardio-respiratory arrest,	3 YO M who died due to cardiopulmonary arrest on day 1 of oseltamivir. He was resuscitated without avail.
6017687	23-Dec-08	1-Feb-07	15.0	Female	US	pneumonia necrotising,pulmonary alveolar haemorrhage,death,hypotension,	15 YO F who experienced hypotension, necrotizing pneumonia, extensive alveolar hemorrhage and died while receiving oseltamivir for influenza a. She presented to PCP who ruled out group a streptococcus and on an unknown date was rx'ed oseltamivir. Three days later the patient died due to necrotizing pneumonia and alveolar hemorrhage. Causality not assessed but see autopsy.
6119869*	16-Mar-09		4.0	Male	JP	encephalopathy,	4 YO with no medical history developed pyrexia 2 days PTA. LFTs increased. Diagnosed with Reye's syndrome. Liver biopsy showed deposit of lipid droplets in hepatocytes.
6168020	27-Apr-09	21-Apr-09	6.0	Male	EG	death,	6 YO who was treated with oseltamivir for avian influenza. No significant PMH. No cause of death reported.
6176291	1-May-09	13-Oct-07	12.0	Male	ID	leukopenia,respiratory failure,lymphopenia,thrombocytopenia,pneumonia,	12 YO M who was treated with oseltamivir for avian influenza. He died of pneumonia 14 days after indirect exposure to poultry. He was treated as an outpatient for 5 days, but then required hospitalization.
6179881	5-May-09	15-Aug-06	9.0	Female	ID	avian influenza,pneumonia,	9 YO F who died of pneumonia and avian influenza. 11 days after onset of symptoms, patient was hospitalized and was started on oseltamivir. Died on day 2 of oseltamivir therapy due to pneumonia. Tamiflu was ongoing at time of death.
6186763	12-May-09		1.5	Male	ID	leptospirosis,death,respiratory failure,	18 month old who was infected with avian influenza presented for tx and received oseltamivir 9 days after hospitalization. He required mechanical ventilation. Experienced psychiatric symptoms as course of symptoms. Leptospirosis diagnosis was made.

Table F2: Line Listing of Pediatric (0 to 16) Death AERS Cases with FDA Receive Date from June 1, 2007 through December 15, 2011. (n=112)

ISR #	FDA Receive Date	Event Date (if known)	Calculated Age (years)	SEX	Country	reported preferred terms (PTs)	Case Summary
6192054	15-May-09		1.0	Unk	US	pathogen resistance,	One year old who required hospitalization for respiratory failure. He was DNR and died due to flu complications.
6192687	18-May-09	19-Mar-06	5.0	Male	ID	thrombocytopenia,psychiatric symptom,pneumonia,influenza,haematocrit decreased,	5 YO M who was treated with oseltamivir for avian influenza was enrolled in study NV22158. he had exposure to poultry and developed influenza-like symptoms. He developed neuropsych symtoms, respiratory failure, and CXR confirmed infiltrates and pneumonia He died due to pneumonia.
6291037	30-Jul-09	28-Sep-08	12.0	Female	US	acute respiratory distress syndrome,septic shock,pneumothorax,cardio-respiratory arrest,ventricular tachycardia,	12 YO F who experienced PNA and was transferred to ICU on (b) (6) with UGIB and respiratory failure. She required intubation and ventilation. One week later she was + for influenza A and started on oseltamivir. She died on day 2 of therapy 2/2 septic shock and ARDS thought to be related to oseltamivir. [Other ISRs in this case # report that drug-event causality is unrelated.
6313946	18-Aug-09		16.0	Female	EG	acute respiratory distress syndrome,pathogen resistance,pneumonia,	Patient died from ARDS 4 days after starting oseltamivir. Thought to due to resistant influenza strain. Drug event causality is not reported.
6314425	19-Aug-09	11-Aug-09	7.0	Female	IN	multi-organ failure,	7 YO female who experienced multi-organ failure while on oseltamivir for H1N1 influenza. On same day she was started on oseltamivir, she developed a 'pneumonic patch' and multi-organ failure 5 days later and died. She required ventilation. No drug-event causality provided.
6314430	19-Aug-09		13.0	Female	IN	lower respiratory tract infection viral,	Patient developed viral pneumonitis and breathlessness. Started on oseltamivir after testing positive for H1N1 influenza. She died on day 5 of hospitalization due to viral pneumonitis. No drug- event causality was noted.
6316849	20-Aug-09	2-Aug-09	15.0	Female	BR	respiratory failure,death,	August 2009 the patient started oseltamivir. Limited information as to if oseltamivir was ongoing at time of death. No drug-event causality.
6316850	20-Aug-09	5-Aug-09	12.0	Female	IL	respiratory arrest,cardiac arrest,	Literature case: 12 YO F patient who experienced cardiac arrest and respiratory arrest 4 days after discharge from hospital H1N1 influenza. No drug-event causality was made with oseltamivir. It's unknown if patient was on oseltamivir at time of death.

Table F2: Line Listing of Pediatric (0 to 16) Death AERS Cases with FDA Receive Date from June 1, 2007 through December 15, 2011. (n=112)

ISR #	FDA Receive Date	Event Date (if known)	Calculated Age (years)	SEX	Country	reported preferred terms (PTs)	Case Summary
6326742	25-Aug-09	27-Feb-07	14.0	Male	JP	abnormal behaviour,fall,	Patient took one dose of tamiflu and fell from the 11th floor.
6326830	25-Aug-09	18-Aug-09	0.6	Female	IN	acute respiratory distress syndrome,pneumonia viral,	Patient was admitted for meningitis and excessive sleep syndrome. She died after an unknown period of time from starting oseltamivir due to ARDS and bronchopneumonia.
6327564	25-Aug-09	6-Aug-09	1.0	Female	GB	cardiac arrest,shunt occlusion,	1 YO who experienced shut occlusion and cardiac arrest while on oseltamivir for unkonwn indication. Med history included pulmonary atresia. Concomitant meds included ASA. Shunt occlusion may be due to hypercoagulation. No drug- event causality with oseltamivir made.
6329140	26-Aug-09	1-Jul-09	15.0	Female	BR	cardio-respiratory arrest,septic shock,pneumonia,bronchopneumonia,infection,	15 YO F who was found to be negative x 2 for H1N1 Influenza. She was rx'ed oseltamivir for prevention [dose NOS] and required hospitalization for 6 hours and diagnosed with pneumonia and prescribed azithromycin. She traveled on a plane and required CPR x 30 min to no avail.
6337581	2-Sep-09		4.0	Female	CO	gastrointestinal haemorrhage,	Limited information on a pediatric patient with experienced fatal GIB while on oseltamivir for influenza. She died on an unknown date after starting oseltamivir (influenza was improving).
6347157	10-Sep-09	21-Aug-09	6.0	Male	TW	multi-organ failure,	6 YO male patient who was treated for H1N1 influenza died of multi-organ failure. He was found to be + for H1N1 on 7/27/09 and died on (b) (6) He was started on oseltamivir despite poor prognosis.
6359767	17-Sep-09	2-Sep-09	16.0	Male	IN	cardiac infection,pneumothorax,	16 YO M who was started on oseltamivir was 'was doing fine' then developed pneumothorax and heart infection and died 17 days after hospital admission. Limited information.
6366454	21-Sep-09	8-Sep-09	5.0	Male	IN	pulmonary oedema,	5 YO M who was treated for 2009 H1N1 influenza. He required hospitalization and ventilation. He developed pulmonary edema and died 5 days after hospitalization. There was limited information to assess a drug-event causality with oseltamivir and death/pulmonary edema.
6413394*	26-Oct-09	13-Oct-09	4.0	Male	JP	encephalitis,	4 YO M developed s/sx of influenza and was started on oseltamivir within 48 hours of symptoms. She developed convulsions on way home from medical office and was admitted. Developed decreased BP, respiratory arrest, required intubation and a respirator. Declined with ARF and decreased

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							urine output. Died 8 days after diagnosis of influenza of acute encephalatitis. No drug-event causality was provided.
6417586*	28-Oct-09	12-Oct-09	16.0	Male	JP	encephalopathy,	16 YO F who died of influenza encephalopathy. He was prescribed zanamivir and diagnosed with influenza encephalopathy and subsequently prescribed oseltamivir. He experienced cardiac arrest and was started on mechanical ventilation in ICU. He died of influenza encephalopathy which started prior to oseltamivir administration.
6422889	2-Nov-09	16-Oct-09	7.0	Male	KR	acute respiratory failure,	7 YO M who required hospitalization for pneumonia and pneumothorax. 8 days later he was started on oseltamivir for influenza. He discontinued therapy after 5 days died 11 days after discontinuing oseltamivir due to acute respiratory failure. No drug- event causality was reported.
6424536	3-Nov-09	22-Oct-09	3.0	Male	JP	disease progression,	3 YO M with influenza started on oseltamivir on day 2 of symptoms. He required ER care with unsuccessful CPR and he died (b) (6).
6437296	12-Nov-09	29-Oct-09	6.0	Female	JP	disease progression,	6 YO Female who had signs/symptoms of influenza and was prescribed oseltamivir on day 2 of symptoms. That same day she developed cardio-respiratory arrest at the clinic and was unsuccessfully treated. The reporter stated that progression of underlying disease was not related to oseltamivir use.
6437298	12-Nov-09	31-Oct-09	8.0	Female	JP	cardiac failure,	8 YO Female with influenza. On day one of treatment she developed convulsions and CV arrest. CPR was unsuccessful and patient died.
6442730	17-Nov-09	7-Nov-09	3.0	Male	JP	brain death,	3 YO M with influenza started on oseltamivir on day 2 of symptoms. He required ambulance care with unsuccessful CPR . He died due to brain death secondary to influenza. No drug-event causality was provided.
6446287	19-Nov-09	Nov-09	5.0	Female	JP	disease progression,	5 YO with influenza like illness. On day 2 of symptoms she had a convulsion and then presented to outpatient clinic and received oseltamivir rx. Hours later she experienced cardiopulmonary arrest and died. Reporter suspected involvement of influenza for death.

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ISR #	**FDA Receive Date**	**Event Date (if known)**	**Calculated Age (years)**	**SEX**	**Country**	**reported preferred terms (PTs)**	**Case Summary**
6446289	19-Nov-09	9-Nov-09	3.0	Female	JP	pneumonia,	3 YO F with co-infection of influenza and pneumonia. She has a MH of chronic respiratory disease. She was ventilated, then admitted to ICU, started on oseltamivir and died due to acute pneumonia all on the same day. Reporter did not provide a drug-event causality.
6450328	23-Nov-09	9-Nov-09	2.0	Male	JP	pneumonia influenzal,	Two year old male who developed H1N1 influenza virus infection, experienced pneumonia which progressively worsened necessitating a ventilator.He died of influenza associated pneumonia despite oseltamivir treatment. FDA reviewer was unable to establish a causal link between death and oseltamivir exposure.
6463944	1-Dec-09	11/9/2009	16.0	Female	KR	rhabdomyolysis,renal failure acute,multi-organ failure,	Media report of a sixteen year old female who was infected with the 2009 H1N1 influenza virus who developed rhabdomyolysis, acute renal failure and multi-organ failure concurrent with oseltamivir treatment. FDA reviewer was unable to establish the role oseltamivir may have played in the death of this teenager.
6473852	4-Dec-09	22-Nov-09	4.0	Female	TW	influenza,	Four year old female who became infected with 2009 H1N1 influenza virus whose condition worsened requiring hospitalization and use of two different neuraminidase inhibitors (oseltamivir and zanamivir). On an unspecified date she succumbed to influenza. FDA reviewer unable to establish a causal role between death and oseltamivir exposure.
6479981	8-Dec-09	3-Nov-09	2.0	Male	KR	disease progression,	2 YO with H1N1 influenza died due to disease progression. No drug-event causality provided.
6479983	8-Dec-09	8-Nov-09	6.0	Male	KR	disease progression,	Six year old male who became infected with 2009 H1N1 influenza virus and progressed to fatal disease the day oseltamivir treatment was started. FDA reviewer was unable to establish a causal link between death and oseltamivir exposure.
6483168	9-Dec-09	30-Nov-09	2.0	Male	JP	disease progression,	2 YO started on oseltamivir as outpatient and required transfer to hospital same day due to cardiopulmonary arrest. No drug-event causality was reported.
6486694*	10-Dec-09	1-Jan-09	1.0	Male	JP	cardiac failure,renal failure,encephalopathy,	1 YO patient who was diagnosed with influenza. CT scan showed mild cerebral atrophy, patient was intubated, admitted to ICU. When transferred to general wards developed renal failure and cardiac failure. He died 20 days after transfer to general wards due to acute necrotic encephalopathy and

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							renal/cardiac failure. No drug-event causality reported.
6486696	10-Dec-09	1-Jan-09	5.0	Female	JP	pneumonia influenzal,	5 YO with H1N1 influenza required ventilation and died due to respiratory failure secondary to disease.
6486732	10-Dec-09	2-Dec-09	0.0	Male	JP	disease progression,	Male patient under the age of 10 with H1N1 2009 Influenza who experienced disease progression while on oseltamivir and died on day 2 of oseltamivir therapy. No other information was provided. FDA reviewer: Limited information to assess drug-death causality.
6507026*	21-Dec-09	1-Nov-09	3.0	Female	JP	encephalopathy,	3 y F, fever/cough/abd pain/rigors x 1 d. + H1N1, tamiflu started; decreased LOC; decompensated died. No attribution reported
6521427	30-Dec-09			Male	JP	sudden death,respiratory depression,	5 y M, presented with fever, H1N1 +, 2 doses Tami, each dose followed by hypoxemia. Vented, sudden death after dose #2. No Autopsy
6521458*	30-Dec-09	21-Dec-09	3.0	Female	JP	encephalopathy,	3 y F, fever H1N1, prog resp failure. Death attributed to H1N1, not oseltamivir.
6531561	8-Jan-10	1-Dec-09	16.0	Female	IL	influenza,	Newspaper article report of 16 year old girl who had concurrent cancer and H1N1 influenza infection, who succumbed to her influenza infection.
6534018*	12-Jan-10	31-Dec-09	1.0	Male	JP	encephalopathy,	Toddler who developed seizures and fever with influenza A infection. He was hospitalized and diagnosed with encephalopathy which lead to his death.
6538930*	15-Jan-10	4-Jan-10	4.0	Male	JP	brain oedema,encephalopathy,cerebral haemorrhage,cardiovascular disorder,respiratory failure,blood pressure decreased,disseminated intravascular coagulation,status epilepticus,circulatory collapse,	Child who had sudden onset of fever, who rapid tested positive for influenza A virus, developed status epilepticus and was subsequently diagnosed with influenza encepaholpathy. CT revealed significant cerebral edema and hemorrhage. He also developed DIC concurrently. Death attributed to influenza encephalopathy.
6540676*	18-Jan-10	9-Jan-10	8.0	Male	JP	encephalopathy,	Child who developed fever and began "speaking in tongues" was admitted to the hospital for pneumonia-like symptoms. He was rapid test positive for influenza A so oxygen and

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							oseltamivir were started. He developed decreased level of consciousness with encephalopathy and died secondary to influenza encephalopathy.
6541555	19-Jan-10	1-Oct-09	5.0	Male	JP	myocarditis,sudden death,pneumonia,respiratory depression,	Literature report: Patient died from pneumonia and myocarditis. The reporter dud not provide a drug-event causality. Respiratory depression noted after each dose of oseltamivir and was attributed as due to oseltamivir given a temporal association.
6570053	4-Feb-10	22-Jan-10	1.6	Female	BR	drug ineffective,pneumonia,	Journalist report of 19 month old female who died despite treatment with oseltamivir (lack of efficacy) for suspected H1N1 influenza infection. She died due to pneumonia.
6583203	16-Feb-10	8-Feb-10	15.0	Male	JP	myocarditis,	Teenage male who developed a fever and sore throat that progressed to respiratory arrest at home resulting in hospitalization in the ICU. Diagnosed with H1N1 influenza and died after an extended ICU stay. Cause of death believe to be acute myocarditis.
6596413	23-Feb-10	1-Dec-09	1.0	Male	HK	drug ineffective,	Toddler with a history of congential heart disease who was admitted to a hospital with complicated influenza. He required ventilation and an ICU stay. He continued to deteriorate and succumbed to influenza and his preexisting heart disease.
6608244	1-Mar-10	27-Nov-09	9.0	Female	GB	pancytopenia,	Development of pancytopenia and death in a 9 year old girl, with a complicated medical history of cystic fibrosis and colonized infection who had recently received oseltamivir, an inactivated influenza vaccine dose and SMX/TMP.
6638212*	17-Mar-10	23-Nov-09	13.4	Male	JP	reye's syndrome,	Reported feels that acute encephalopathy [reye's syndrome] was due to oseltamivir. Patient with history of Vitamin B6 deficient epilepsy. A possibility that clonic spasm was a symptom of vitamin b6-dependent epilepsy could not be ruled out. A possibility that acetaminophen induced reye's syndrome could not be ruled out.
6646176*	23-Mar-10	21-Sep-09	7.0	Male	JP	encephalopathy,shock haemorrhagic,	7 YO male patient who experienced influenza encephalopathy while on oseltamivir for treatment use. He required ICU admission. On day 2 he was transferred to another hospital in the peds ward, developed hypothermia and died. Pleural effusion, loss of BP control, respiratory and circulatory status were aggravated and patient died.

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6651458*	25-Mar-10	4-Mar-10	8.0	Female	JP	multi-organ failure,	Child who developed fever and altered level of consciousness with influenza infection. She required ICU admission with ventilation. She developed encephalopathy and renal failure then subsequently died from these complications from her influenza.
6668907	6-Apr-10	27-Mar-10	16.0	Female	BR	death,	Teenage female who developed fever and cough at home that was treated with home remedies. She eventually was hospitalized for viruses and thrombocytopenia was diagnosed. She had a cardiac arrest and respiratory insufficiency and died. Cause of death was not clearly established.
6706947	3-May-10	24-Sep-04	9.0	Female	TH	influenza,	Nine year old female who contracted avian influenza and subsequently died. Dead poultry around her home were observed. Her influenza symptoms began with a fever that rapidly progressed to cough and difficulty breathing. She was hospitalized requiring intubation/ventilation. She developed leukopenia and thrombocytopenia concurrent with oseltamivir therapy and she was treated throughout her hospital stay until her death. FDA reviewer believes disease more likely to have contributed to this patient's demise that oseltamivir.
6715653	7-May-10	2009	1.5	Female	US	death,pathogen resistance,respiratory failure,neutropenia,organising pneumonia,cytomegalovirus infection,	Toddler (18 months) female who was admitted for relapsed hematologic malignancy and subsequently developed in influenza like symptoms on hospital day #2. She was placed on oseltamivir for influenza A and B co-infections, but she soon developed oseltamivir resistance (H275Y mutation) with the type A virus and began IV zanamivir compassionate use. Despite prolonged treatment with neuraminidase inhibitors, she continued to shed virus (likely because of chronic immunosuppression) and she died on hospital day #57 of progressive respiratory insufficiency from her influenza infection. FDA reviewer believes disease more likely to have contributed to this patient's demise that oseltamivir or zanamivir.
6790425*	24-Jun-10	6-Oct-09	5.0	Male	JP	encephalopathy,	5 YO male without underlying disease was noted to have signs/symptoms of influenza and started on oseltamivir one day later. He developed convulsions, vomiting, consciousness disorder and was admitted with brain edema. CP arrest occurred and patient died after resuscitation. No drug-event causality was made.

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6801472	29-Jun-10	12-Jun-10	1.0	Male	IN	death,	One year old with H1N1 influenza infection which ultimately led to an ICU admission. He received oseltamivir for the infection, yet the details of the case are scant. FDA reviewer is unable to establish a causal link between the death and drug exposure.
6860385	20-Jul-10	19-Oct-04	14.0	Female	TH	influenza like illness,thrombocytopenia,leukopenia,pneumonia,respiratory failure,	Teenage female who developed fever, cough and shortness of breath that progressed respiratory insufficiency requiring mechanical ventilation. She raised poultry and this was a confirmed avian influenza infection. Chest x-ray showed infiltrates consistent with acute pneumonia. She received oseltamivir late in the course of infection and died due to pneumonia. FDA reviewer could not establish a causal link between oseltamivir exposure and the death.
6876722	27-Jul-10	18-Jul-10	10.0	Female	BR	death,	Ten year old female with a history of asthma who became infected with H1N1 influenza A virus. Report is scant on details other than asthma exacerbated her clinical course and she eventually died. The FDA reviewer was unable to establish a causal link between death and oseltamivir exposure.
6876844	27-Jul-10	11-Jul-10	0.9	Male	IN	H1N1 influenza,	Infant (11 months) with a history of nephrotic syndrome who was infected H1N1 influenza A virus and hospitalized. He died during the hospitalization with no details provided of the events leading up to the death. FDA reviewer could not establish a causal link between death and oseltamivir exposure.
6876851	27-Jul-10	16-Jul-10	14.0	Female	IN	disease progression,	Teenage female who became infected with H1N1 influenza A virus and developed a high fever and eventually died in the hospital of disease progression. Details are scant in this report. FDA reviewer was unable to establish a causal link between death and oseltamivir exposure.
7001108	20-Sep-10	2-Feb-04	4.0	Male	TH	death,	Four year old boy who contracted avian influenza developed progressive respiratory difficulty which required intubation. Evidence of acute pneumonia on x-ray. He also experienced cardiac failure requiring inotropes. Apparently, three days after requiring intubation, he was removed from the ventilator and discharged home where he died on the same day of unknown causes. FDA reviewer cannot establish a causal link between the drug exposure and the death in this case.

Table F2: Line Listing of Pediatric (0 to 16) Death AERS Cases with FDA Receive Date from June 1, 2007 through December 15, 2011. (n=112)

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7001141	20-Sep-10	7-Dec-05	5.0	Male	TH	death,	Five year old boy who contracted avian influenza developed progressive respiratory difficulty which required intubation. Evidence of acute pneumonia on x-ray. One week prior to the onset of respiratory symptoms, he had directly handles poultry and avian influenza was known to be circulating in the region. He had symptoms for several days before seeking medical advice causing a delay in oseltamivir initiation. His disease progressed and he eventually succumbed. FDA reviewer cannot establish a causal link between the drug exposure and the death in this case.
7007843	22-Sep-10	29-Jan-04	12.0	Male	TH	death,avian influenza,	Twelve year old male who became infected with avian influenza and developed influenza-like respiratory symptoms requiring hospitalization. He was exposed to slaughtered or processed poultry. No evidence that he required an ICU stay. Details in the report are scant, but apparently he was discharged and died on the same day. FDA reviewer was unable to establish a causal link between death and oseltamivir exposure.
7022352	30-Sep-10	1-Jan-09	6.0	Male	JP	pneumonia,acute respiratory distress syndrome,	6 YO M admitted for treatment of pneumonia. Eventually required ventilation and was found to have influenza. Died from pneumonia.
7074017	29-Oct-10		0.0	Unk	NL	pathogen resistance,pulmonary function test decreased,	The outcome of resistant H1N1 influenza was not reported. The HCP assessed the events of fatal deterioration of lung function and oseltamivir resistance as related to oseltamivir. FDA reviewer: Pathogen resistance is a labeled event with oseltamivir, an anti-viral agent.
7074175	29-Oct-10	Not reported	5.0	Male	US	death,	Media report of a five year boy infected with 'swine flu' who also was diagnosed with leukemia and immunosuppressed. Potential duplicate to ISR 7091144 but too few details to verify as a duplicate report. Because of his immune impairment, he was at increased risk of developing a drug resistant infection and he did. He eventually died of from influenza complications. FDA reviewer could not establish a causal link between death and oseltamivir exposure.
7125540	29-Nov-10	Not reported	13.0	Female	IN	drug ineffective,shock,	Thirteen year old female with osteosarcoma and a solitary lung metastasis on chemotherapy who became infected with H1N1 influenza virus, who progressively deteriorated requiring mechanical ventilation and inotropes to sustain life. She did not

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							respond to early initiation of oseltamivir. FDA reviewer could not establish a causal link between death and oseltamivir exposure in this patient.
7177190	20-Dec-10	9-Nov-09	7.9	Male	NL	arthritis,electrolyte imbalance,sepsis,toxicity to various agents,acute lymphocytic leukaemia,death,arrhythmia,	Seven year old boy who developed influenza and was prescribed oseltamivir, influenza vaccine and oral diclofenac as treatment. He subsequently developed a "reactive arthritis" and ALL. Based on the report, he did not appear to have a complicated influenza course. He died secondary to ALL.
7179543	21-Dec-10	11-Nov-09	1.0	Male	FI	pneumonia,	Media report of a one year old male who became infected with H1N1 influenza virus and developed a subsequent fatal pneumonia despite treatment with oseltamivir. FDA reviewer was unable to establish a causal link between death and oseltamivir exposure.
7179601	21-Dec-10	7-Jan-04	6.0	Male	US	aspartate aminotransferase abnormal,pneumonia,thrombocytopenia,leukopenia,anaemia,alanine aminotransferase abnormal,influenza like illness,respiratory failure,	Six year old male who was exposed to slaughtered and/or processed poultry, who developed avian influenza A infection. He initially experienced mild symptoms that progressed to respiratory insufficiency requiring inotropes and intubation. Chest xray revealed bilateral pneumonia. Oseltmaivir was given late in the course of the illness. FDA reviewer is not able to establish a link between oseltamivir exposure and this child's demise.
7179605	21-Dec-10	23-Mar-07	2.5	Male	US	multi-organ failure,pancytopenia,pneumonia,pathogen resistance,	Thirty month old male who had influenza like symptoms between March and August 2007 and shed virus throughout this interval. He was treated with oseltamivir intermittently throughout this period. He required chemotherapy to treat a chronic disease. In August 2007, he progressively worsened from mild influenza symptoms to respiratory insufficiency requiring intubation and he developed multi-organ system failure.
7179665	21-Dec-10	1-Jan-04	7.0	Male	TH	cardiac failure, gastrointestinal haemorrhage, leukopenia, influenza, aspartate aminotransferase abnormal, respiratory failure, pneumothorax, lymphopenia, alanine aminotransferase abnormal,	Seven year old male who became infected with avian influenza virus, who initially developed mild symptoms such as cough, fever, pharyngitis, excessive sputum production that progressed to ventilator dependent breathing difficulty. He also required inotropes for cardiac output. Oseltamivir was used as a therapy but the patient succumbed to progressive respiratory disease. FDA reviewer was unable to establish a causal link between death and oseltamivir exposure.

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7250403	28-Jan-11	17-Feb-09	2.8	Female	ID	acute respiratory distress syndrome, pneumonia,	Two year old female who died after becoming infected with avian influenza. She initially experienced mild influenza symptoms that progressively worsened necessitating ventilatory and inotrpic support to sustain life. FDA reviewer could not establish a causal link between death and oseltamivir exposure.
7290788	14-Feb-11		16.0	Female	TW	influenza,	16 y F, with 4 day hx of fever, cough, unspecified Abx went to hospital for worsening symptoms. Influenza B diagnosed oseltamivir/unspec antibiotics given. Pt died cause not reported. Causality assessment death due to Influenza B unrelated to Tami
7296146	16-Feb-11	20-Jan-09	14.0	Female	ID	pneumonia, acute respiratory distress syndrome,	14 year old, presented with 'influenza symptoms', neuro symptoms (not specified), cough/SOB, progressed to increased LFTs, decreased platelets/WBC. Pneumonia. 7 days after symptoms started + test for influenza (type not known), Received 1 dose of oseltamivir and died 1 day later due to ARDS. No causality assessment provided.
7301898	18-Feb-11	23-Jun-10	13.0	Female	ID	acute respiratory distress syndrome, pneumonia,	Thirteen year old female who contracted avian influenza and progressively deteriorated to pneumonia/ARDS. She was exposed to dead poultry at home. She required mechanical ventilation and inotropes to support life. Despite treatment with oseltamivir, she died due to respiratory failure. FDA reviewer was unable to establish a causal link between death and oseltamivir exposure.
7301962	18-Feb-11	2-Feb-09	12.0	Male	ID	acute respiratory distress syndrome, renal impairment, pneumonia,	12 y M, with fever, pharyngitis, headache, vomiting. Presented on symptom day 8 with tachypnea, low platelet/WBC, Influenza (type not reported). 2 days later started Tami, pulm status worsened, followed 1 day later by renal dys(fx) and pneumonia. Died. Causality not assessed.
7303742	21-Feb-11	20-Mar-09	2.8	Male	ID	respiratory failure, influenza, pneumonia,	Two year old male who developed avian influenza that started as fever and respiratory symptoms that progressively worsened to ventilator dependent respiratory failure. He had pneumonia and did not respond to oseltamivir treatment. Apparently he was discharged on oseltamivir day #7 and died on that same day. The report is not clear on the patient's condition at discharge. FDA reviewer could not establish a causal link between death and oseltamivir exposure.

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7303790	21-Feb-11	28-Jan-11	0.2	Male	TW	H1N1 influenza,	2 m M, ex-30 week premie) treated with Tami and other unspecified antiviral agent (uncertain) due to cough/fever/H1N1. "Died of H1N1" no other causality addressed
7305850	22-Feb-11	5-Mar-09	4.0	Female	ID	acute respiratory distress syndrome,	4 year old female with a 2 day history of headache and cough which progressed over 3 more days to pneumonia and difficulty breathing. H5N1 diagnosed. Oseltamivir/ceftriaxone started and she died the same day from ARDS/respiratory failure. No causality assessment provided.
7311096	24-Feb-11	28-Apr-10	4.0	Female	ID	acute respiratory distress syndrome,	Four year old female who became infected with avian influenza virus and progressed from mild symptoms to ventilator dependent respiratory failure. She died despite treatment with oseltamivir. FDA reviewer could not establish a causal link between death and the oseltamivir exposure.
7311121	24-Feb-11	2-Feb-09	12.0	Male	ID	renal impairment, pneumonia, acute respiratory distress syndrome,	12 y M; decompensating respiratory status/Cytokine storm/ARF; Oseltamivir start/end date can not be determined
7311122	24-Feb-11	27-Feb-09	5.0	Female	ID	acute respiratory distress syndrome,	5 y F, died of ARDS/MOSF, H5N1, untreated first 9 days
7320791*	28-Feb-11	11-Jan	3.0	Male	US	hallucination, abnormal behaviour, encephalitis influenzal,	3 year old male, presented with Influenza B (presenting symptoms not reported). Returned to primary care provider with confusion and disorientation. Transferred to hospital and died with influenza encephalitis. No causality assessment regarding oseltamivir provided. No more information.
7321057	28-Feb-11	27-Feb-09	8.0	Male	ID	anaemia,leukopenia,thrombocytopenia,pneumonia,respiratory failure,	8 y M, seen at Clinic and ER on first day of flu-like symptoms with vomiting and fever. Decompensated 5 days later with worsening respiratory status (^ WOB) and pneumonia. Oseltamivir started on day 9 and N5N1 diagnosis on day 10. Causality assessment not provided.
7496458	23-May-11		1.0	Female	KR	acute respiratory distress syndrome,pathogen resistance,drug ineffective,pneumonia,	1year old female, presented fever, respiratory symptoms, death attributed to drug resistance.
7519152	23-May-11	11-Jan-10	5.3	Male	NL	cytomegalovirus viraemia,lower respiratory tract infection,rhinovirus infection,hypoxia,acute respiratory distress syndrome,multiple-drug resistance,drug	5 y/o M, with ALBL had influenza H1N1 at onset of chemotherapy (no symptoms reported at that time). 10 days after transplant viral load increase and started on Oseltamivir/Peramavir/Ribavarin. Did well initially with low

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						level decreased,respiratory failure,viral mutation identified,pneumonia viral,infection in an immunocompromised host,	viral loads initially, but develope lower respiratory symptoms 3 wks later and died from progressive Influenza/CMV associated RDS. viral isolates at this time were multidrug resistant.
7618300	18-Jul-11		1.0	Female	ES	pathogen resistance,drug ineffective,	1 y F, with leukemia died due to "oseltamivir reistant H1N1" after ? days oseltamivir therapy No other info available
7618303	18-Jul-11		3.0	Male	ES	pathogen resistance,drug ineffective,	3 y M, with leukemia died due to "oseltamivir reistant H1N1" after 15 days oseltamivir therapy. No other info available.
7618304	18-Jul-11		2.0	Female	ES	pathogen resistance,drug ineffective,	2 y F, with Best's disease & unspecified mitochondrial disease presented with 'symptoms of influenza A (H1N)". Started Tam 3 days later. Needed ICU care for resp status. Died due to "oseltamivir reistant H1N1" after ? days oseltamivir therapy. No other info available
7633270	25-Jul-11	Feb-01	2.0	Female	US	drug ineffective,gastrointestinal haemorrhage,pathogen resistance,respiratory distress,	2 y F with MML and unrelated cord cell transplant. 2 wks post transplant exposed to Infl B and oseltamivir started. Influenza symptoms started 4 days later. Symptoms progressed and patient die from progressive respiratory distress, GI bleeding, resistant viral isolate.
7636104	26-Jul-11		13.0	Female	VN	drug ineffective,pathogen resistance,	13 y F, presented with fever, cough, and exposure to H5N1 (not resistant). Started on Tami. Stable x 3 days, then rapid Pulm decomp and died. This patient's viral isolate was oseltamivir Resistant. No causality re: oseltamivir included.
7682915	15-Aug-11		6.0	Female	BR	H1N1 influenza,	6y F, died with H1N1 during oseltamivir treatment. Insufficient information to assess.
7740108	9-Sep-11		14.0	Female	TH	drug ineffective,pathogen resistance,	14 y F, with SLE and corticosteroid therapy. Clinical course not provided other than, pneumonia/progressive respiratory failure, and post mortem detection of oseltamivir resistant strain.
7762139	20-Sep-11	Jul-09	0.1	Unk	US	peritoneal haemorrhage,abdominal compartment syndrome,	22 d, ? Gender, Death from comorbidities not likely related to oseltamivir. No more info
7762145	20-Sep-11	15-Jan-11	9.0	Male	JP	cardio-respiratory arrest,	9 y M, with history of cardiac disease (type unknown), developmental delay, and deafness presented to hospital with fever 39C. Oseltamivir started. Patient found in cardio-

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							respiratory failure 2 days later. CPR failed. Causality not assessed/not assessable.
7762159	20-Sep-11	Jul-09	0.1	Unk	US	hepatic failure,disseminated tuberculosis,	47 d, ? Gender, Hyper-bili, complications of miliary TB. Death due to TB rather than oseltamivir. No more info.
7762163	20-Sep-11	1-Jan-11	16.0	Male	IL	respiratory failure,multi-organ failure,cardiac disorder,	15 year old male, presented to ER with fever chest pains, progressive respiratory difficulty, 'cardiac difficulty'. Admitted and diagnosed with influenza B. Oseltamivir and antibiotics started, died 1 day later. Reported assessed respiratory/card failure/death due to flu not oseltamivir No other information. Patient died of complications from pre-existing co-morbidities (abdominal compartment syndrome, hernia of diaphragm, hemoperitoneum)/

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/s/

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