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TO: Pediatric Advisory Committee

SUBJECT: Tamiflu (oseltamivir phosphate) Pediatric Safety Update: Background Summary and Review of Clinical Review Team Activities, 2007 to Present

Background

This May, 2012 Pediatric Advisory Committee (PAC) meeting represents the fourth PAC discussion of pediatric adverse events (AEs) reported in association with Tamiflu, a neuraminidase inhibitor used for treatment and prophylaxis of influenza. Since the Committee has several new members who were not present at the last meeting presentation in 2007, this document will provide a historical review of the previous discussions and summarize more recent information and the Division of Antiviral Product's (DAVP) ongoing activities to monitor safety of Tamiflu in pediatric patients. Summary information regarding earlier PAC meetings is abstracted from the background memo prepared for the 2007 meeting.

Pediatric Advisory Committee meeting, November 18, 2005

Tamiflu capsules and oral suspension were initially approved in October, 1999, and December, 2000, respectively, and granted pediatric exclusivity under BPCA on March 22, 2004. As part of BPCA requirements, a public safety update for Tamiflu covering the first year of pediatric drug use after granting exclusivity was presented to this committee in November, 2005. At that meeting, the Office of Surveillance and Epidemiology (OSE) focused their review on cases of pediatric deaths and serious adverse events (SAEs) reported to the FDA Adverse Event Reporting System (AERS) database and a summary of drug usage in pediatric patients ($\leq$ 16 years of age) reported from March 22, 2004 through April 22, 2005.

The initial OSE review identified eight pediatric deaths during the targeted period (all from Japan) and 75 unduplicated AE cases (69 from Japan, 5 from U.S., and 1 from

Canada). The two categories of AEs that were reported most often and were most concerning included skin/hypersensitivity reactions and neuropsychiatric events. Twelve cases of skin/hypersensitivity reactions were identified in pediatric patients including events such as Stevens-Johnson syndrome, anaphylactoid reactions, erythema multiforme, and toxic epidermal necrolysis. These skin reactions appeared unlikely to be related to influenza illness and the Tamiflu label was revised later that year to include precautionary language regarding severe skin reactions.

Another 32 cases of neuropsychiatric AEs were reported in the pediatric age group including cases of delirium, abnormal behavior, hallucinations, convulsions, encephalitis, and others. Many of these reports provided insufficient detail to make clear assessments of causality but the pattern of the neuropsychiatric event reports from Japan was unusual. Several possible explanations for the increased reporting of neuropsychiatric AEs from Japan were explored including: differences in pharmacokinetic profile or drug metabolism in Japanese patients, differences in the manifestations of influenza in Japanese patients, differences in dosing or use of Tamiflu in Japan compared to the U.S. (e.g., increased number of Tamiflu users in Japan providing an early signal of events that had not yet occurred in the U.S.), and increased surveillance or reporting of AEs in Japan.

A number of additional steps were taken to evaluate a possible causal association between Tamiflu and the neuropsychiatric AEs. The integrated safety database from all submitted pediatric clinical trials of Tamiflu was reanalyzed; no safety signal for neurologic toxicity was identified in that process. A review of submitted clinical pharmacology data and of the clinical pharmacology literature revealed no identifiable differences between Asian and Caucasian individuals in terms of oseltamivir pharmacokinetic profile or metabolism. No specific information suggested possible genetic differences that might have a differential impact on AEs.

Potential explanations for the neuropsychiatric AEs were provided by differences in the rate of use of Tamiflu (Japan accounted for about 75% of the Tamiflu prescriptions worldwide), differences in methods of AE reporting (Japanese regulatory authorities required more active solicitation of AEs following drug approvals or major labeling changes), and differences in the manifestations of influenza illness in Japan compared to the U.S. (Japan reports more severe influenza-associated encephalitis than other countries). In response to national awareness of influenza-associated encephalitis, rapid testing for influenza and treatment of illness in pediatric patients were recommended as part of standard health care in Japan and were reimbursed by their national health insurance.

The 2005 PAC agreed with the FDA that there was insufficient evidence to establish that the neuropsychiatric AEs represented a safety signal associated with Tamiflu use. We concluded that these events were more likely reflective of increased AE reporting from Japan, increased use of the drug in that population, and an increased awareness of neurologic manifestations of influenza. However, we could not exclude that similar events might be reported in the U.S. if use of Tamiflu increased substantially in pediatric patients. The Agency committed to providing an update on the neuropsychiatric AEs

after one to two additional influenza seasons and continued enhanced monitoring including real-time review of AEs reported during influenza season and regular discussions between DAVP and OSE. The PAC requested a follow-up within 2 years. They agreed with the general approach and asked for additional information at the time of the update regarding analysis of AEs during Tamiflu prophylaxis, data on pharmacokinetics, pharmacogenomics, drug metabolism, or effects of CNS inflammation, reviews of large healthcare claims databases, and information regarding natural history of influenza and its complications, and management of influenza in pediatric patients in Japan.

Pediatric Advisory Committee meeting, November 16, 2006

At the 2006 meeting of the PAC, OSE presented a brief update to their initial review of the neuropsychiatric AEs. This presentation was intended to inform the committee of ongoing reporting during the year since the first presentation but did not undertake a full reanalysis of the events. During the additional influenza season, use of Tamiflu continued to be much more prevalent in Japan, with that country accounting for over 7.1 million prescriptions in 2006 (through the time of the review) compared to 1.8 million in the U.S.

An additional 5 pediatric deaths were reported from November, 2005, to November, 2006, including 2 U.S. cases. One of the U.S. deaths occurred in an 8 year old many months after a severe episode of Stevens-Johnson syndrome and the other occurred in an otherwise healthy 3 year old who developed "severe strep pneumonia" with subsequent respiratory and cardiac arrest. Three Japanese patients' deaths were related to apparent self-injurious behavior (e.g., falling/jumping from balcony, running into traffic) in adolescents shortly after receiving their first dose of Tamiflu. These reports focused attention on the neuropsychiatric AEs particularly events described as abnormal behavior or delirium.

The updated review of neuropsychiatric AEs identified 129 AERS reports in all age groups (range 1 ½ to 90 years) in the intervening year. Of these 129 reports, 103 (95 from Japan, 5 from U.S., 3 from other countries) contained case descriptions that were complete enough to evaluate and were not confounded by concurrent medical or psychiatric disorders. These cases were reviewed individually and divided into one of eight categories based on the most prominent symptoms or findings in the report. Cases were categorized as:

- Delirium with prominent behavioral disturbances – 60 total cases (1 U.S.)
- Suicidal events – 6 (1 U.S.)
- Panic attack – 3
- Delusions – 3
- Convulsions – 12 (1 U.S.)
- Depressed level of consciousness – 4 (1 U.S.)
- Loss of consciousness – 4 (1 U.S)
- Miscellaneous – 9 (1 U.S.)

The 60 cases in the category described as delirium with prominent behavioral disturbances were among the most unusual. Many of these cases reported events of hallucinations or abnormal behavior accompanied by a "fright/flight" response that led to injury and many occurred in adolescents or pre-adolescents who had received only one or two doses of Tamiflu. While some of these cases were accompanied by high fever, some patients were reported to have no or minimal fever at the time of the AE. The reports of delirium with prominent behavioral disturbances had a stereotypical quality that was remarkable although it was difficult to determine if this was a result of similarity among the events or a result of the translation process.

At the time of the 2006 PAC no new data provided insight into the etiology of these neuropsychiatric events and significant uncertainty remained regarding a causal relationship between Tamiflu and the reported AEs. Because of the continued reporting of these events from Japan, a small number of U.S. cases, and the increasing number of cases of delirium with abnormal behavior, DAVP and OSE recommended the following precautionary language for the Tamiflu label (approved November, 2006):

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

DAVP felt that the risk/benefit assessment at that time favored not recommending that patients discontinue medication without first contacting a healthcare provider. The 2006 PAC concurred with the previous committee's request for an extensive analysis including (1) a report by the sponsor on neuropsychiatric events; (2) a request for FDA to invite Japanese experts to report on their experience and provide Japanese data on the extent of prophylactic use and AEs in their population.

Pediatric Advisory Committee meeting, November 27, 2007

DAVP and OSE continued real-time AERS case monitoring for all approved antiviral drugs during the 2006-2007 influenza season. Although no noticeable changes in the types or pattern of neuropsychiatric AEs reported in association with the use of Tamiflu, the number of cases continued to increase. The 2007 OSE review again focused on pediatric deaths and neuropsychiatric AEs but in this review the pediatric age range was expanded to 21 years of age and also included similar AE analyses for other approved influenza antiviral drugs.

Using the AERS database, OSE identified a cumulative total of 25 deaths from all causes reported in patients $\leq$ 21 years of age receiving Tamiflu. Three of the deaths occurred in the U.S., 21 were reported from Japan, and 1 was reported from Egypt (an avian influenza case). Five of the deaths (all reported from Japan) involved adolescent patients

who died from traumatic injuries suffered as a result of falls or running into traffic. Not all of the deaths were witnessed but they were considered to represent part of the spectrum of neuropsychiatric AEs including delirium, hallucinations, and impulsive/injurious behavior. Some of these events were reported as "suicides" in the Japanese press although we received no information suggesting that any were purposeful acts with an intention to harm.

The OSE cumulative review of neuropsychiatric AEs reported in association with Tamiflu use included 596 unduplicated cases across all ages, including 16 deaths with a neuropsychiatric event. Of these, 365 cases (including 6 deaths) occurred in patients ≤ 21 years of age. The OSE reviewers again conducted a broad search of the AERS database for neuropsychiatric AEs including searching for accidental injuries that might have been precipitated by abnormal behavior. Cases were reviewed individually and assigned to one of 9 categories, a refinement of the system used for the 2006 safety update. The following summary table of pediatric neuropsychiatric AEs by age and category is taken from the 2007 OSE review.

Table 1: Categories of Neuropsychiatric Adverse Events Reported with Tamiflu Use by Age – Cumulative through May 31, 2007

	Pediatric (≤ 21 years)			Adult (> 21 years)	Age Unknown	Total
	< 1	1-12	13- 21			
ANX	--	1	1	5	2	**9**
DIB	--	23	25	11	--	**59**
DEL	--	134	41	46	4	**225**
DEL + SZ	--	4	1	--	--	**5**
DLC	--	9	8	17	1	**35**
LOC	1	9	9	31	--	**50**
MSC**	--	26	17	47	20	**110**
PAN	--	--	2	4	1	**7**
SUI	--	1	2	9	--	**12**
SZ	4	30	16	31	2	**83**
SZ + DLC	--	--	--	1	--	**1**
Total	**5**	**242**	**122**	**202**	**30**	**596**

ANX - Anxiety/fear without hallucinations; **DIB**-Delirium w/ impulsive behavior & injury; **DEL**-Delirium, delusion, hallucination, psychosis; **DLC -** Depressed level of consciousness (from lethargy to coma); **LOC** – Loss of consciousness, incl. syncope; **MSC** – Miscellaneous (insomnia-23, abnormal behavior not specified-9, night terrors-8, unusual speech-5, agitation-5, confusion-5, somnolence-4, amnesia-4, dizziness-3, excitement-3, myoclonus-3, sleepwalking-2, and insomnia with agitation-2); **PAN -** Panic attacks, panic disorder; **SUI** - Suicidal events (including suicidal ideation); **SZ** - Seizures, convulsions.

A noticeable spike in U.S. AE reporting occurred in November, 2006, after the 2006 PAC meeting and before the 2006-2007 influenza season peaked. Similarly, after Japanese media reports of 2 adolescent deaths during the winter of 2007, there was a substantial spike in neuropsychiatric AE reports from Japan. Those reports prompted a thorough review of Tamiflu usage and safety by the Japanese Ministry of Health, Labor and

Welfare (MHLW) and in April, 2007, the MHLW issued new labeling for Tamiflu, restricting its use in pediatric patients between 10 and 19 years of age.

To provide additional context for the 2007 Tamiflu review, OSE undertook a review of all antiviral drugs approved for treatment or prophylaxis of influenza including amantadine, rimantadine, and zanamivir (Relenza, another neuraminidase inhibitor). Both amantadine and rimantadine are known to be associated with neurologic adverse events (e.g., seizures) and these events are described in the U.S. package inserts. Amantadine is specifically labeled with a warning regarding suicide attempts. Because of resistance among influenza strains, very little use of amantadine and rimantadine occurred after 2006 and few pediatric AEs were reported for these drugs. However, during the 2006-2007 influenza season a dramatic increase was observed in reports of neuropsychiatric AEs reported in association with use of Relenza. These reports are also predominantly Japanese in origin and the majority involved patients $\leq$ 21 years of age. These reports were reviewed individually and categorized similar to the Tamiflu review (see Table 2).

Table 2: Categories of Neuropsychiatric Adverse Events Reported with Zanamivir (Relenza) Use by Age – Cumulative through May 31, 2007

	Pediatric (≤21 yrs)		Adults (> 21 yrs)	Age Unknown	Total
	0-12 yrs	13- 21yrs			
ANX	0	0	1	0	**1**
DIB	5	1	1	0	**7**
DEL	41	13	5	2	**61**
DLC	2	1	0	0	**3**
LOC	0	2	9	2	**13**
MSC	**3**	3	10	2	**18**
PAN	0	0	0	0	**0**
SUI	0	0	0	0	**0**
SZ	2	1	8	1	**12**
Total	**53**	**21**	**34**	**7**	**115**

ANX-Anxiety, fear without Hallucinations; **DIB**-Delirium w/impulsive behavior & injury
DEL-Delirium, delusions, hallucinations, psychosis; **DLC**-Depressed level of consciousness
LOC-Loss of consciousness, incl. syncope; **MSC**- Miscellaneous (insomnia-5, nightmares-2, other events - 1 each); **PAN**-Panic attacks, panic disorder; **SUI**-Suicidal events (incl. ideation); **SZ**- Seizures, convulsions.

The neuropsychiatric AEs reported with Relenza, which qualitatively were very similar to those reported in association with Tamiflu, cast more uncertainty on the role of the drugs in development of these AEs. Like Tamiflu, Relenza is an influenza neuraminidase inhibitor but it is administered as a dry powder for inhalation. Pharmacokinetic studies of orally inhaled zanamivir indicate that approximately 4-17% of the inhaled dose is systemically absorbed and the blood-brain barrier is expected to further decrease central nervous system (CNS) exposure to zanamivir. In addition, the timing of the Relenza AE case reports suggested a spike in usage and AE reporting shortly after a public alert in

Japan regarding the association of neuropsychiatric AEs with Tamiflu that was followed by restrictions on Tamiflu use.

A review of the scientific literature prior to the 2007 PAC revealed multiple publications describing neurologic complications of influenza in pediatric patients some of which included a behavioral component. Additional published data showed no apparent differences between Japanese and Caucasian adults in oseltamivir pharmacokinetics. Numerous research groups evaluated possible genetic and biochemical mechanisms to explain the neuropsychiatric AEs but none were confirmed. Reports from health claims database surveys conducted by Roche suggested that Tamiflu use was not associated with increased risk of neuropsychiatric AEs but these results were also not definitive.

At the time of the 2007 PAC, DAVP considered the role of Tamiflu (and Relenza) in the occurrence of neuropsychiatric AEs to be unknown; however, reports of these events continued to accumulate. Neither FDA nor the 2007 PAC could determine whether these events represented a drug class AE, a drug-disease interaction, or a disease manifestation of influenza, but thought healthcare providers should be aware of neuropsychiatric events and parents should be instructed to monitor their children closely when beginning medication for influenza.

The PAC agreed with the FDA plan to continue monitoring AEs for Tamiflu on a monthly basis during flu season and recommended labeling changes to incorporate a description of NP symptoms which might have occurred due to the influenza illness, irrespective of drug therapy; to convey uncertainty in causality of the NP symptoms; to note abrupt appearance of symptoms; and to indicate that "injurious behavior" included fatal outcomes. Similar labeling changes were recommended for the other antiviral influenza medications. Updated precautionary wording regarding neuropsychiatric events and the uncertainty regarding causality was included in the labels for both Tamiflu and Relenza in January, 2008, as follows:

> "Neuropsychiatric Events
> Influenza can be associated with a variety of neurologic and behavioral symptoms which 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 delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving Tamiflu. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made but they appear to be uncommon based on Tamiflu usage data. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of Tamiflu to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient."

Monitoring and Review Activities - 2007 to Present

Following the 2007 PAC meeting, DAVP and OSE staff continued monthly reviews of AERS cases reported during influenza season. The 2007-2008 influenza season was characterized by the emergence of a strain (A/H1N1) that was resistant to Tamiflu but sensitive to the adamantanes (amantadine and rimantadine). Another strain (A/H3N2) circulating that season remained susceptible to Tamiflu and resistant to amantadine and rimantadine, prompting CDC to recommend treatment with potentially multiple drugs in some patients. This pattern of seasonal influenza and treatment recommendations continued during the 2008-2009 influenza season complicating the review of AEs as patients might have received a combination of antiviral drugs.

Beginning in April, 2009, a novel triple-reassortant influenza A/H1N1 emerged in Mexico and rapidly spread around the world. The WHO identified the spread of 2009 H1N1 as a pandemic in June, 2009. The new strain was susceptible to Tamiflu and Relenza but not to amantadine or rimantadine and CDC moved quickly to recommend treatment with the neuraminidase inhibitors for a wide range of patients potentially at risk for serious complications of influenza, including pregnant women, children younger than 2 years of age, and patients with certain underlying medical conditions (e.g., asthma/chronic lung disease, neurologic/neurodevelopmental conditions, diabetes).

DAVP and OSE increased the frequency of AE monitoring during the pandemic period in anticipation of greatly increased drug usage and additionally asked Roche to provide monthly summaries of AEs reported to the company. Because the CDC guidelines recommended treatment of high risk patient groups not adequately studied in clinical trials, Roche was asked to specifically collect and review all AEs in pregnant women, pediatric patients younger than 1 year of age, and elderly patients older than 65 years of age.

Roche's final Pandemic Safety Report was submitted in June, 2010, and summarized AEs reported to the company between May 1, 2009 and December 31, 2009. The report evaluated the safety profile of Tamiflu during the pandemic reporting period compared to the pre-pandemic period (before May 1, 2009). The most reliable comparison of pre- and pandemic AEs used reporting data from the U.S. and Japan because data from these countries were most consistent across the periods. Selected AEs were targeted for evaluation including: increased international normalized ratio (INR), pancreatitis, hepatic failure, respiratory complications, neuropsychiatric events, and GI events (nausea, vomiting and diarrhea). Certain subpopulations were highlighted including: patients older than 65 years, infants younger than 1 year, pregnant women, infants exposed via breast milk, immunocompromised patients, and those receiving Tamiflu for prophylaxis.

In the Pandemic Safety Report, a general assessment of reported AEs showed the lower limit of the 95% CI for rate ratio calculation (RR) was > 1 for 20 high level descriptive terms, i.e., the events were reported more frequently during the pandemic period than before. Among the high level terms reported more often during the pandemic period

were: “overdoses,” “medication errors,” and “maladministrations.” Respiratory complications were reported more often during the pandemic period with an RR of 2.29 (lower bound of 95% CI 1.76). Cases with fatal outcome comprised 2.1% of all global reports in the pre-pandemic period compared to 7% of reports during the pandemic period.

Among the AEs of special interest, there were too few events of hepatic failure or other fatal hepatic events, pancreatitis, and increased INR reported to allow useful comparison between the periods. Neuropsychiatric events were reported during both periods. The upper bound of the 95% CI for rate ratio was < 1 for the US/Japan population during the pandemic period suggesting lower reporting during that time. Except for an increased rate of events suggestive of severe influenza illness during the pandemic period, the AE profile of the pre-pandemic and pandemic periods appeared to be similar. This aspect of the report was also consistent with FDA monitoring; no new safety signal was identified. However, the report confirmed FDA concerns (based on our monthly AE monitoring) that some patients had difficulty understanding dosing instructions, particularly for Tamiflu oral suspension, leading to medication errors.

The FDA evaluated the issue of medication errors related to dosing Tamiflu oral suspension (12 mg/mL) prior to and during the pandemic period. Dosing errors appeared to be related to a combination of factors including: frothing of the commercial Tamiflu oral suspension when it was shaken making dosing less accurate, use of a Tamiflu-specific dosing device marked in milligram increments rather than widely used milliliter-marked devices, and differences in concentration between commercial suspension and pharmacist-compounded suspension. The FDA discussed these issues with Roche and agreed that they could be eliminated or significantly improved with relatively simple changes. In March, 2011, we approved a new concentration of Tamiflu oral suspension, 6 mg/mL, which had been used in pediatric clinical trials and did not become frothy when shaken. Dosing recommendations were converted to volumetric units allowing a standard oral syringe marked in milliliters to be used. The instructions for emergency compounding by pharmacists were also revised to provide a suspension of similar concentration (6 mg/mL). The new concentration suspension was released for distribution prior to the 2011-2012 flu season along with communications to healthcare providers and pharmacists to explain the change in concentration.

Near the end of the 2009 H1N1 pandemic, DAVP and OSE staff received a draft manuscript proposing a potential drug-drug interaction between sotalol, a cardiac anti-arrhythmic drug, and Tamiflu that might result in prolonged QT interval and torsade de pointes. Sotalol has previously been associated with QT prolongation and is labeled accordingly. The accumulated clinical pharmacology data related to Tamiflu suggested a significant drug-drug interaction was unlikely but a specific oseltamivir/sotalol interaction study was not available. The OSE reviewer searched the AERS database and the scientific literature for cases possibly representing torsade de pointes among patients receiving Tamiflu. Eleven case reports were identified between 2000 and 2009, 7 of which were reported from the U.S. Most of these cases involved patients with documented coronary artery or other cardiac disease and were further confounded by

concomitant use of other medications known to be associated with QT prolongation such as sotalol, clarithromycin, pirmenol, moxifloxacin and amiodarone. Although the OSE review did not suggest an association of Tamiflu and QT prolongation or a significant drug-drug interaction between Tamiflu and sotalol, DAVP requested Roche submit additional relevant data. The sponsor provided results of a previously conducted study evaluating potential QT effects of Tamiflu in which doses of 75 mg, 225 mg, and 450 mg of Tamiflu or placebo were administered twice daily for 5 days. Although the study did not include the positive control arm currently recommended by FDA, no effect on electrocardiogram parameters, including QT interval, were observed with any dose, including the supra-therapeutic 450mg dose (exposures achieved up to 7-fold therapeutic levels).

Throughout the pandemic, DAVP staff participated in weekly pandemic influenza conference calls with other HHS agencies monitoring the progression of the pandemic, clinical manifestations and complications of influenza being reported, evolving treatment and vaccination recommendations, and adverse event reporting.

According to the CDC website summary of statistics for the 2009-2010 influenza season, "During the 2009 H1N1 pandemic and the 2009-10 influenza season, the percentage of deaths attributed to pneumonia and influenza (P&I) exceeded the epidemic threshold for 11 consecutive weeks from September 27 to December 12, 2009, and again for three consecutive weeks from January 10 to January 30, 2010. The percentage of P&I deaths peaked twice, once at 8.1% during the week ending November 21, 2009, and again at 8.2% during the week ending January 23, 2010." CDC's summary of 2009 H1N1 cases and related hospitalizations for the pandemic period (April 2009 to March 2010) estimated that among patients from birth to 17 years of age there were 14-28 million cases of 2009 H1N1 and 61,000-127,000 hospitalizations. These statistics must be viewed in the context of a pandemic that, while widespread, resulted in influenza illness that was generally of mild to moderate severity.

As noted in the OSE Drug Use Review, Tamiflu use was higher during the pandemic year than during any year before or since the pandemic. Table 3 displays the estimated annual dispensed prescriptions for Tamiflu from outpatient retail pharmacies over the last 5 years. During this 5-year period, pediatric prescriptions represented 32% to 44% of all Tamiflu prescriptions filled. During the same reporting period, pediatric AE reports accounted for about 28% of AEs reported (crude counts) to the FDA AERS Database (see OSE Pediatric Postmarket Adverse Event Review).

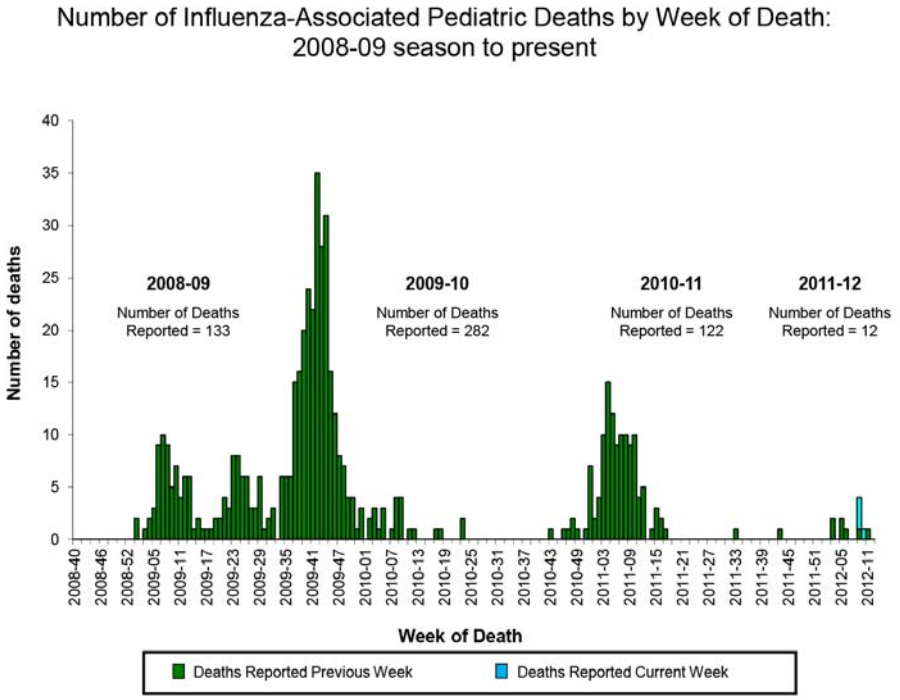
Table 3: Estimated Tamiflu Prescriptions by Year and Age Group

	2007	**2008**	**2009**	**2010**	**2011**
0 to 16 years	696,310	1,107,679	3,245,291	443,371	1,075,599
17 years and older	884,598	2,338,946	4,186,960	650,537	1,594,029

Age not specified	134	59	204	678	896
Total Prescriptions	1,581,042	3,446,685	7,432,455	1,094,585	2,670,524

Source: IMS, Vector One®: National (VONA). Extracted 3-29-12. File: VONA 2012-328 oseltamivir age annually 2007-2011 3-29-12.xls, Courtesy: V. Borders-Hemphill, March 2012.

Influenza activity has been relatively moderate in terms of numbers of patients with reported influenza-like illness and severity of illness over the 2010-2011 and 2011-2012 influenza seasons. However, pediatric deaths attributable to influenza occur during every influenza season and have been a nationally notifiable event reported to the CDC since 2004. The following graph from the CDC's website weekly influenza surveillance report depicts these pediatric deaths since the 2008-2009 influenza season, reported throught March 24, 2012.



Since the 2007 PAC meeting, DAVP and OSE staff have reviewed numerous manuscripts and published articles related to seasonal and pandemic influenza, Tamiflu and its safety/toxicity profile, the safety/toxicity profile of other approved influenza antivirals, and possible mechanisms of presumed drug toxicity. Because of the added length, a complete listing of these articles is not included with this memo but can be provided to Advisory Committee members on request. To date, none of the published literature provides a clear explanation for whether the neuropsychiatric AEs reported with

Tamiflu and other neuraminidase inhibitors are attributable to drug, influenza disease, or an interaction of drug and disease in a specific sub-population.

Summary

Cases of neuropsychiatric and other AEs continue to be reported in association with Tamiflu but the increased number of reports during the 2009 H1N1 pandemic appears to be commensurate with the increased use of the drug during that period. Although rates of specific events can not be accurately determined from passively collected AERS data, serious AEs occur uncommonly based on estimates of drug usage. No new safety signals were identified during the current review of pediatric AEs and no specific safety changes to labeling are recommended by the clinical review team. DAVP and OSE will continue to monitor reported AEs and the scientific literature for more definitive evidence of a causal relationship between Tamiflu and the previously reported neuropsychiatric events.