

MEMORANDUM

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

DATE: November 9, 2007

TO: Office of Pediatric Therapeutics
Pediatric Advisory Committee Members

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SUBJECT: **Pediatric Safety Update for Tamiflu
DAVP Review Team Background Memo**

I. Background

This meeting represents the third Pediatric Advisory Committee discussion of 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 original presentation in 2005, this document will first provide a historical review of the previous discussions and then summarize new information and the FDA's current thinking regarding the safety of Tamiflu in pediatric patients.

Pediatric Advisory Committee meeting, November 18, 2005

Tamiflu capsules (NDA 21-087) and oral suspension (NDA 21-246) 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) presented their review of the Adverse Event Reporting System (AERS) database for all safety reports related to Tamiflu in patients ≤ 16 years in the one-year period following granting pediatric exclusivity. The OSE consult focused on review of deaths, serious AEs, and drug usage in pediatric patients 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 adverse event (AE) cases (69 from Japan, five from U.S., and one from Canada). A total of 12 pediatric deaths were reported since approval of Tamiflu. 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 and the pattern of the neuropsychiatric event reports from Japan were unusual. In order to determine whether these reports constituted a safety risk for U.S. pediatric patients, OSE, the DAVP Review Team, and the Office of Counterterrorism and Pediatrics (OCTAP) undertook a thorough evaluation. 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. (eg. increased number of Tamiflu users in Japan giving a preview of events that have 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 but no 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 Tamiflu pharmacokinetic profile or metabolism. At that time, there was no specific information available regarding 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, differences in methods of AE reporting, and differences in the manifestations of influenza illness in Japan compared to the U.S. The OSE review of drug usage in the U.S. and data on worldwide usage provided by Roche in 2005 revealed that Tamiflu was prescribed far more frequently in Japan than in the U.S. As of 2005, Japan accounted for about 75% of the Tamiflu prescriptions worldwide (about 24.5 million). It became clear that millions of pediatric patients in Japan were receiving rapid diagnostic testing for influenza and subsequently receiving Tamiflu. Also, it was learned that the Japanese regulatory authorities required more active solicitation of AEs following drug approvals or major labeling changes than is provided by the AERS spontaneous/passive reporting. All of these solicited AE reports collected by Roche's Japanese affiliate were subsequently submitted to the AERS database.

A review of the pediatric scientific literature was undertaken by the DAVP Clinical Reviewer and the OCTAP Medical Officer. At that time, no literature reports were found of neurologic or neuropsychiatric AEs specifically related to use of Tamiflu but numerous reports of encephalitis and encephalopathy related to influenza were reviewed. The majority of these citations over the last 10 years were from Japanese authors where the entity of acute

influenza-associated encephalopathy and encephalitis had been recognized since the mid-1990s. This syndrome was characterized in a series of national surveys of pediatric practitioners and hospitals.

In a retrospective study of the 1998-99 influenza season, Morishima et al, investigated 217 reported cases of influenza-associated encephalopathy or encephalitis in pediatric patients and identified 148 that met a case definition of encephalopathy with documented influenza. The typical course of these patients included the rapid onset of high fever, seizures, and altered consciousness, with rapid progression to coma within one to two days of initial flu-like symptoms. Although both types of influenza were represented, 88% of encephalopathy cases were associated with influenza A. Consequences of encephalopathy in their population were severe with 32% mortality and 28% “disability” in this series. Although most of these series focused on severe encephalitis, some reports identified specific patterns of “delirious behavior” and hallucinations in children with influenza. Some more recent reports suggested that the rates of influenza-associated encephalitis/encephalopathy have been declining in Japan. To date, there is no consensus as to whether influenza-associated encephalitis/encephalopathy is really more common among Japanese children or why these neurologic events seem to be recognized more often in that population. However, partly in response to this awareness, rapid testing for influenza and treatment of illness in pediatric patients were recommended as part of standard health care in Japan and were covered by national health insurance.

A presentation by Roche, the sponsor for Tamiflu, highlighted the general safety profile of Tamiflu and provided an overview of global drug usage. The sponsor presented the results of health claims database analyses that suggested that Tamiflu did not result in excess neuropsychiatric outcomes but did confer a survival benefit in a large cohort of predominately adult influenza patients. The sponsor also noted that many of the cases of neuropsychiatric AEs included other complicating factors that could have contributed to the events, such as high fever or concomitant medications.

At the 2005 Advisory Committee meeting the Agency concluded 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. The Advisory Committee agreed with this general approach and asked for the following information at the time of the update:

- Information from Roche regarding analysis of AEs during Tamiflu prophylaxis compared to treatment
- Information regarding Tamiflu experience in other countries
- Estimate of incidence rates of neuropsychiatric AEs

- Any additional pharmacokinetic, pharmacogenomic, drug metabolism, or effects of CNS inflammation data that might pertain to these AEs
- Information regarding AEs gleaned from reviews of large health care claims databases
- Information regarding natural history of influenza, complications of influenza, and management of influenza in pediatric patients in Japan

Pediatric Advisory Committee meeting, November 16, 2006

At the 2006 meeting of the Advisory Committee, OSE presented a brief update to their initial review of the neuropsychiatric AEs. This presentation was intended to inform the committee of on-going 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 five pediatric deaths were reported from November, 2005, to November, 2006, including two U.S. cases. Of the two U.S. deaths, one death 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. The additional deaths from Japan focused attention on the abnormal behavioral component identified in some patients. Three Japanese patients’ deaths were related to apparent self-injurious behavior (eg., falling/jumping from balcony, running into traffic) in adolescents who had received a single dose of Tamiflu.

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, five from U.S., three from other countries) contained case descriptions that were complete enough to evaluate and were not confounded by concurrent medical or psychiatric disorders. In this cohort, three cases involved prophylactic use of Tamiflu. The three prophylaxis cases were either confounded (ie., drug administered for prophylaxis but with stated flu-like symptoms) or did not include events of delirium or abnormal behavior.

Case reports were identified by a search of the AERS database that included > 30 high-level reporting terms for neurologic, psychiatric, and behavioral AEs. These cases were reviewed individually and divided into one of eight categories based on similar descriptions.

Categories were assigned 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 Advisory Committee there were no new data that provided insight into the etiology of these neuropsychiatric events. There was still significant uncertainty regarding any causal relationship between Tamiflu and the reported AEs. However, primarily because of the continued reporting of these events from Japan, now with a small number of U.S. cases, and the increasing number of cases of delirium with abnormal behavior, DAVP and OSE recommended changes to the Tamiflu label following the 2005-2006 influenza season. In November, 2006, the following wording was incorporated into the PRECAUTIONS section of the label:

“Neuropsychiatric Events

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

The labeling revisions were presented to the Advisory Committee for comment. Some members of the committee suggested that the labeling should include a recommendation for caregivers to stop Tamiflu treatment and contact a health care provider if abnormal behavior occurred. DAVP felt that the risk/benefit assessment at that time favored not recommending that patients discontinue medication without first contacting a health care provider.

II. 2007 Update - Office of Surveillance and Epidemiology Review of Adverse Events

DAVP and OSE continued real-time safety report monitoring for all approved antiviral drugs during the 2006-2007 influenza season. While there have not been 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 current OSE review, “Tamiflu (oseltamivir) – Safety Update on Neuropsychiatric Events: Review of Neuropsychiatric Events with Other Antiviral Products,” includes AE cases from the time of Tamiflu approval in October, 1999, through May 31, 2007, the end of the latest influenza season (allowing a lag period for delayed reporting). As in previous reports, the current review focuses on pediatric deaths and neuropsychiatric AEs but in this review the pediatric age range was expanded to 21 years of

age in order to be most inclusive. In order to better understand the profile of AEs associated with Tamiflu, the current review also includes similar AE analyses for other approved influenza antiviral drugs.

Using the AERS database, OSE has identified a cumulative total of 25 deaths from all causes reported in patients ≤ 21 years of age receiving Tamiflu. Three of the deaths occurred in the U.S., 21 were reported from Japan, and one 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 from windows or balconies or running into traffic. Some of these deaths were not witnessed but likely represent part of the spectrum of neuropsychiatric AEs that includes 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 these were purposeful acts with an intention to harm.

The OSE cumulative review of neuropsychiatric AEs reported in association with Tamiflu use includes 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, with 242 events reported among patients ≤ 12 years of age. The great majority of these cases (when specified) were reported for the indication treatment of influenza with only 19 cases (6 in patients ≤ 21 years of age) reported in association with the prophylaxis indication.

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 neuropsychiatric AEs by age and category is taken from the OSE review with the pediatric cases highlighted.

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
	5	242	122	202	30	596

Total						
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- ANX** - Anxiety/fear without hallucinations
- DIB**-Delirium w/ impulsive behavior & injury
- DNI**-Delirium, delusion, hallucination, psychosis
- DPR** - 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
- SE** - Suicidal events (including suicidal ideation)
- SZ** - Seizures, convulsions

Although the overall pattern of events does not appear to have changed significantly over the last three influenza seasons, there have been some noticeable events that appear to have affected reporting. As noted at the 2005 and 2006 Advisory Committee meetings, most of the AE reports originate from Japan. In reality, there were only five neuropsychiatric AE reports from the U.S. in all age groups as of the 2006 Advisory Committee update. With the publicity generated by that meeting, we noticed a spike in U.S. AE reporting in November, 2006, well before the 2006-2007 influenza season peaked. After Japanese media reports of two 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 and in April, 2007, the MHLW issued new labeling for Tamiflu, restricting its use in pediatric patients between 10 and 19 years of age.

III. Review of Other New Information

OSE Reviews of AE Reporting for Other Antiviral Drugs

In order to provide a more complete overview of the neuropsychiatric AEs, OSE undertook a review of all antiviral drugs approved for treatment or prophylaxis of influenza including amantadine, rimantadine, and zanamivir (Relenza). Both amantadine and rimantadine are known to be associated with neurologic adverse events (eg., seizures) and are labeled accordingly and amantadine is specifically labeled with a warning regarding suicide attempts. Because of recent shifts in influenza strain susceptibility patterns, the Center for Disease Control and Prevention has warned health care providers against using amantadine and rimantadine during the last two influenza seasons and usage has decreased. One pediatric neuropsychiatric AE with prominent abnormal behavior similar in nature to those reported with Tamiflu use was identified in the review of rimantadine. None were identified in association with amantadine. For further details regarding the safety review of these two drugs, please refer to the OSE consult sections, “Neuropsychiatric Cases with Symmetrel® (amantadine hydrochloride)” and “Neuropsychiatric Cases with Flumadine® (rimantadine hydrochloride).”

During the 2006-2007 influenza season a dramatic increase was observed in reports of neuropsychiatric AEs reported in association with use of Relenza, another neuraminidase

inhibitor. These reports are also predominately Japanese in origin and the majority involves patients ≤ 21 years of age. These reports were reviewed individually and assigned a neuropsychiatric AE category, similar to the process conducted for Tamiflu case reports. Table 2 was taken from the OSE review and summarizes the neuropsychiatric AEs reported with the use of Relenza according to age and category.

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 cast more uncertainty on the role of drugs in these AEs. Although there were no deaths reported in association with Relenza use, the neuropsychiatric AEs were otherwise very similar to those reported in association with Tamiflu. 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. It is postulated the blood-brain barrier would further decrease central nervous system (CNS) exposure to zanamivir, although there is no available animal or human data that explores this issue. In addition, the timing of the Relenza AE case reports suggested that there had been a sudden spike in usage and AE reporting shortly after a public alert in Japan regarding the association of neuropsychiatric AEs with Tamiflu and following restrictions on Tamiflu use. For additional details regarding the neuropsychiatric AEs associated with Relenza, please refer to the OSE consult, "Neuropsychiatric Cases with Relenza™ (zanamivir)."

In addition, OSE reviewers conducted reviews of four health claims database studies submitted by Roche in response to the 2005 Advisory Committee request for additional

comparisons of Tamiflu to other drugs or no treatment. For a more detailed description of these studies and concerns related to study design and methodology, please refer to the OSE consult, “Epidemiological Analysis of Four Health Claims Database Studies” and the addendum, “Analyses of Neuropsychiatric Events in Health Claims Database Studies submitted on October 29, 2007.” All of these studies used large health insurance or Medicare claims databases and attempted to link diagnosis of influenza, use of Tamiflu, and selected outcomes. Results may not be generalizable to populations without health insurance who may have less access to health care but, overall, the databases represented large, diverse populations.

Two of the health claims database studies were retrospective analyses primarily of influenza-related mortality and the complications of pneumonia and myocardial infarction but two studies provided more detailed analyses of neuropsychiatric outcomes. The report, “Study of the Impact of Oseltamivir on the Risk of Pneumonia and Other Outcomes, 2000 – 2006,” evaluated rates of pediatric and adult respiratory outcomes and hospitalizations (using MarketScan Commercial Claims and Encounters and Medicare Supplement and COB databases) stratified according to vaccination status and whether Tamiflu was prescribed or no antiviral was documented. The authors concluded that use of Tamiflu decreased the risk of respiratory outcomes, particularly in pediatric patients (≤ 12 years) and hospitalization in adults (≥ 13 years). The authors also evaluated the rates of selected cardiac and neuropsychiatric events in the population (all ages). In this analysis of neuropsychiatric outcomes combining all age groups, the authors concluded that use of Tamiflu was not associated with increased risk of any neuropsychiatric events. The study report by Wilcox and Zhu, “Neuropsychiatric Events among Influenza Patients” used data from the UnitedHealthCare health plans databases to assess neuropsychiatric events, also without regard to age. Their original analysis also suggested that Tamiflu use was not associated with risk of neuropsychiatric events.

For both of these studies, however, independent OSE review of the methodology and results raised a number of questions regarding the strength of the conclusions. The most glaring deficiency was a lack of stratification by age in both study reports. The OSE reviewers requested additional clarifications and analyses. A reanalysis by the authors of the Wilcox and Zhu study was recently submitted providing stratification by age (≤ 17 years vs. > 17 years). In that analysis, it appeared that Tamiflu use was associated with increased risk for “affective psychoses” (adjusted OR 1.69, 95% CI 1.13, 2.53). However, it should be noted that this was the only association identified among multiple comparisons and some concerns about the original methodology and study design remain. Roche also submitted their own repeat analysis combining the two databases. Their new analyses provided better assurance of adequate matching between the comparison groups, analysis of more types of events, and stratification by age (≤ 17 years vs. > 17 years). The new analysis revealed no significant differences in neuropsychiatric events between patients receiving Tamiflu and those receiving no antiviral therapy.

Additional Information from the Scientific Literature

Since the initial reports of neuropsychiatric AEs associated with Tamiflu use were publicized, investigators have explored a variety of hypotheses regarding the etiology of these events. None of these hypotheses have been proven to have clinical relevance but are summarized here for completeness.

Clinical Pharmacology Data:

A Roche-supported clinical pharmacology study compared the PK profile of Tamiflu in adult Japanese and Caucasian subjects receiving 75 mg, 150 mg, or placebo twice daily for 7 days. A total of 28 subjects, 14 Japanese and 14 Caucasian, were enrolled. In each ethnic group, six subjects received each of the two dose levels and two subjects received placebo. As might be expected, Caucasian subjects were larger than the Japanese subjects by a mean of 10 cm in height, 20 kg in weight, and 3.7 kg/m² in BMI. In spite of the differences in weight, the authors conclude there were no clinically significant differences in PK parameters for oseltamivir and oseltamivir carboxylate (the active metabolite) between Japanese and Caucasian subjects. A significant increase in C_{max} among Japanese subjects on Day 1 became less apparent when the PK model accounted for weight and a similar increase was not identified for C_{max} on Day 7. No differences in AEs or laboratory values were identified between the 2 groups. Overall, the data generated in this study were consistent with previously published pharmacokinetic data for Tamiflu (Schentag JJ, 2007).

Clinical Data:

Recent publications shed some light on the differences in rates of hospitalization and neurologic complications between the U.S. and Asian populations. Newland et al reported a 4-year retrospective cohort study of influenza-related neurologic complications (INC) at Children's Hospital of Philadelphia in a large group of patients with laboratory-confirmed influenza. Using hospital virology laboratory records, the authors identified 842 patients with confirmed influenza between June, 2000, and May, 2004. Hospital records of these patients were reviewed for evidence of neurological complications (eg., lumbar puncture or neuroimaging study performed, neurology consult requested, seizure documented in admission, discharge, or billing codes). Detailed chart reviews were subsequently performed. The authors identified 72 patients (8.5%) with INC that were further categorized as influenza-related encephalopathy (8), post-infectious influenza encephalopathy (2), seizures (56), and other complications (6). The most frequent INC were seizures with "febrile seizure" occurring in 27 patients and "other seizure", defined as seizures occurring in patients who had a known underlying neurologic condition, occurring in 21 patients. Acute influenza encephalopathy was documented in 8 (1%) of confirmed influenza patients, one of whom had an underlying neurologic disorder. In this subset of patients, neurologic symptoms emerged within three days of respiratory symptoms and included disorientation, lethargy, visual hallucinations, and speech abnormalities. Two additional patients developed neurologic symptoms six to 14 days after onset of respiratory symptoms and were considered to have a post-infectious influenza encephalopathy. The authors estimated the incidence of INC using a population-based neighborhood cohort and data from the 2000 U.S. Census. The estimated incidence of INC was 4.1 cases per 100,000 child-years. Multivariate analysis suggested that patients < 4 years of age and those with underlying neurologic or

neuromuscular disease were at highest risk to develop INC. Information regarding use of antiviral medications was not presented in the paper (Newland JG, 2007).

In response to Newland's report, a group from the University of Hong Kong published similar data from their hospital. Chung et al, reported that a retrospective review of admissions from March, 1998, to February, 2003, revealed that 20% of children developed INC. In their population of 874 patients with confirmed influenza, 182 developed INC. Of these, 165 patients (90%) had febrile seizure and 5 patients (0.6%) were identified with encephalopathy. They estimated the incidence of INC was about 240 per 100,000 person-years in Hong Kong. The authors speculated that the higher incidence might be related to lower threshold for admission for influenza-related illness in their population (Chung BHY, 2007).

New Hypotheses to Explain Increased Risk of Neuropsychiatric AEs:

Li and other members of a Chinese research team proposed that the preponderance of neuropsychiatric AEs reported from Japan might be related to a nonsynonymous single nucleotide polymorphism (SNP) in human cytosolic sialidase. Human cytosolic sialidase (HsNEU2) is thought to be a homolog of influenza virus neuraminidase. According to the NCBI dbSNP database, R41Q, a SNP near the enzymatic active site of sialidase, was found in 9.3% of Asian population, 0.5% in sub-Saharan African population, but not found in European or African American population. The authors state that structural analyses and *K_i* measurements using *in vitro* sialidase assays suggest that the R41Q SNP could increase binding affinity of human sialidase to oseltamivir carboxylate and reduce sialidase activity. They further postulate that the SNP itself results in lower sialidase activity. They hypothesize that patients homozygous for this SNP would have intrinsically reduced sialidase activity that would be further lowered by Tamiflu administration possibly leading to neuropsychiatric symptoms (Li C-Y, 2007).

The authors note that patients with sialidosis, a rare, hereditary, lysosomal storage disorders, develop a variety of neurologic symptoms as the disease progresses and draw an analogy between patients with this disorder and patients with reported neuropsychiatric AEs. The infantile form of sialidosis may be severe, resulting in dysmorphic features, progressive developmental delay, myoclonic seizures, and hepatosplenomegaly. The juvenile form is less severe but can result in myoclonus, visual impairment (with presence of cherry-red spots), ataxia, and hypotonia. These symptoms do not appear to resemble the neuropsychiatric AEs we have reviewed but clearly neurologic symptoms are prominent in the disorder as glycoprotein complexes accumulate in neurons. It is not clear how a single dose of a drug could result in a similar process.

Another group of investigators also evaluated the neuroexcitatory actions of Tamiflu (oseltamivir) and its metabolite, oseltamivir carboxylate. Izumi Y, et al., used juvenile rats and rat hippocampal slices to evaluate whether oseltamivir has adverse effects on CNS. The authors noted that intraperitoneal injections of oseltamivir alone produced no changes in rat behavior within two hours. However, when rats received oseltamivir prior to injection of ethanol, there were significant increases in ethanol-induced sedation (ie., time to awakening). They also noted that rectal temperatures were lower in rats treated with oseltamivir prior to

ethanol. The authors concluded that oseltamivir could modulate the actions of CNS drugs, “even if oseltamivir alone does not cause behavioral changes.” The authors also evaluated whether oseltamivir altered neuronal function in rat hippocampal slices using a paired-pulse stimulation method. In these experiments, they found that administration of oseltamivir and oseltamivir carboxylate facilitated population spikes and excitatory postsynaptic potentials, measures of neuronal excitation, under certain conditions. They interpret their results to mean that oseltamivir or its metabolite may be responsible for enhanced neuronal excitability. Further they suggest that medications containing ethanol or CNS stimulants taken concurrently with Tamiflu may contribute to behavioral changes (Izumi Y, 2007).

A group of Japanese investigators evaluated the effects of p-glycoprotein (P-gp, a cellular efflux transporter) as a determinant of brain distribution of oseltamivir and oseltamivir carboxylate. These authors used a P-gp overexpressing cell line to evaluate the permeability of oseltamivir across the cells. Permeability was higher in P-gp overexpressing cells in the basal to apical direction than in the opposite direction while wild-type cells exhibited comparable permeability in both directions. In the presence of a P-gp inhibitor, directional transport disappeared. Brain distribution of oseltamivir was increased in P-gp deficient (mdr1a/1b knockout) mice compared to wild-type mice. Oseltamivir carboxylate did not appear to be a substrate of P-gp. The authors conclude that low levels of P-gp activity or drug-drug interactions at the level of P-gp may lead to enhanced brain accumulation of oseltamivir and thereby account for neuropsychiatric AEs (Morimoto K, 2007).

IV. DAVP’s Conclusions and Action Plan

Based on the accumulated data, it remains unclear whether the neuropsychiatric AEs reported with Tamiflu use represent a true drug reaction, an unusual manifestation of influenza, or a drug-disease interaction. While it is possible that these events represent a class effect of neuraminidase inhibitors, it appears unlikely that significant amounts of zanamivir penetrate into the central nervous system and this casts more doubt on the biological plausibility that the neuropsychiatric AEs represent a true adverse drug reaction. There remain questions regarding the preponderance of cases reported from Japan and whether this represents an artifact of a different reporting system or a racial/genetic predisposition to either a drug reaction or a disease process. During previous Advisory Committee meetings, there were few U.S. cases and none reporting the delirium with abnormal, self-injurious behavior. Over the last few influenza seasons use of Tamiflu has increased in the U.S. particularly among pediatric patients. It is possible that the new U.S. cases are a consequence of achieving adequate usage to identify a rare event.

Research into possible mechanisms of increased neuropsychiatric AEs with the use of Tamiflu provides some interesting hypotheses. The hypothesis that Tamiflu (or similar drugs) might enhance the effects of other CNS stimulant drugs is intriguing. Many of the patients reported in the AE cases were receiving other medicinal products but it is impossible to determine whether the use of concomitant medications played a significant role in the events. Similarly, the suggestion that there could be a genetic factor such as a SNP contributing to the demography of the reports is interesting but as yet there is no evidence

linking the SNP to the events. The summaries of recent scientific publications point out that multiple hypotheses are emerging but they all remain speculative and none have been shown to be clinically significant as yet.

At this time, DAVP considers the role of Tamiflu (or Relenza) in the occurrence of neuropsychiatric AEs to be unknown, however, reports of these events continue to accumulate. Regardless of whether they represent a drug class AE, a drug-disease interaction, or a disease manifestation, health care providers should be aware of neuropsychiatric events and parents should be instructed to monitor their children closely when beginning medication for influenza. We agree with OSE that precautionary wording regarding these events should be included in the labels for both Tamiflu and Relenza. We also plan to continue our regular review of the AERS database for AE cases reported with the use of influenza antiviral drugs during the coming influenza season.

V. Reference List

Schentag JJ, Hill G, Chu T, and Rayner CR. Similarity in pharmacokinetics of oseltamivir and oseltamivir carboxylate in Japanese and Caucasian subjects. *J Clin Pharmacol* 2007;47:689-96.

Newland JG, Laurich VM, Rosenquist AW, et al. Neurologic complications in children hospitalized with influenza: characteristics, incidence, and risk factors. *J Pediatr* 2007;150:306-10.

Chung BHY, Tsang AMC, and Wong VCN. Neurologic complication in children hospitalized with influenza: Comparison between USA and Hong Kong. *J Pediatr* 2007; Nov: e17-e18.

Li C-Y, Yu Q, Ye Z-Q, et al. A nonsynonymous SNP in human cytosolic sialidase in a small Asian population results in reduced enzyme activity: potential link with severe adverse reactions to oseltamivir. *Cell Research* 2007;17:357-62.

Izumi Y, Tokuda K, O'Dell KA, Zorumski CF, and Narahashi T. Neuroexcitatory actions of Tamiflu and its carboxylate metabolite. *Neuroscience Letters* 2007;426:54-8.

Morimoto K, Nakakariya M, Shirasaka Y, et al. Oseltamivir (Tamiflu) efflux transport at the blood-brain barrier via P-glycoprotein. *Drug Metab Dispos* 2007;Oct 16 online as doi:10.1124/dmd.107.017699.