PEDIATRIC ADVISORY COMMITTEE BRIEFING DOCUMENT FOR TAMIFLU

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AVAILABLE FOR PUBLIC DISCLOSURE

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GLOSSARY OF ABBREVIATIONS

BPCA	Best Pharmaceuticals for Children Act
CES1	Carboxylesterase 1
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
EEG	Electroencephalogram
FDA	Food and Drug Administration
GPRD	General Practice Research Database
MHLW	Ministry of Health, Labor, and Welfare
OAT1	Organic anion transporter 1
OC	Oseltamivir carboxylate
OP	Oseltamivir phosphate
OR	Odds ratio
PAC	Pediatric Advisory Committee
P-gp	P-glycoprotein
PPI	Patient Package Insert
SOC	System Organ Class
UHC	United Healthcare
US	United States
USPI	United States Package Insert

1. EXECUTIVE SUMMARY

Tamiflu® (oseltamivir phosphate [OP]), an ethyl ester prodrug of a potent and specific inhibitor of the neuraminidase enzyme of influenza virus types A and B, is approved in the United States (US) for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days and for the prophylaxis of influenza in patients 1 year and older.

Since introduction to the global marketplace, about 48 million patients have received Tamiflu. The majority (75%) of these patients are located in Japan (approximately half of whom have been children [17.5 million]), where Tamiflu has been established as the standard of care for confirmed influenza treatment, following the use of a rapid diagnostic test to confirm the nature of the infection.

As required by the Best Pharmaceuticals for Children Act (BPCA), a routine safety review for Tamiflu was conducted by Roche and Food and Drug Administration (FDA) during the year following the granting of pediatric exclusivity. This review focused on pediatric deaths and serious adverse events and the results, as required by the BPCA, were presented to the Pediatric Advisory Committee (PAC) in November 2005. Two clusters of postmarketing reports were identified: serious skin reactions and neuropsychiatric events seen primarily in children in Japan. In response to the postmarketing reports of skin reactions, Roche updated the Precautions section of the US Package Insert (USPI) and the Patient Package Insert (PPI) in December 2005. The consensus of Roche, FDA, and the PAC in November 2005 was that there was insufficient evidence to establish that neuropsychiatric events represented a safety signal for Tamiflu. However, after reviewing reports of neuropsychiatric events in the subsequent flu season, Roche and FDA agreed that it was prudent to be transparent with healthcare professionals about these events and thus, Roche worked with FDA in 2006 to update the Precautions section of the USPI to describe the postmarketing reports of neuropsychiatric events and to recommend monitoring for abnormal behavior (see Section 2.2).

Since its previous meeting with the PAC, Roche has continued its postmarketing surveillance for neuropsychiatric events associated with Tamiflu use and has proactively conducted a number of additional preclinical and clinical studies. The purpose of this document is to update the PAC on Roche's continued pharmacovigilance and due diligence activities. Since 2005, Roche has performed a comprehensive analysis of postmarketing neuropsychiatric adverse events reported globally in children (age ≤ 16 years) for the last two flu seasons using a broad definition for neuropsychiatric events. Roche has also evaluated the potential role of Tamiflu in neuropsychiatric events by evaluating data from its pooled clinical trials of Tamiflu in pediatric patients and data from two US healthcare claims databases, MarketScan and United Healthcare (UHC). In addition, Roche has evaluated the potential role of influenza in neuropsychiatric events by: 1) reviewing literature reports of neuropsychiatric events in influenza patients treated with antivirals other than Tamiflu or no antivirals, 2) reviewing reports to the Japanese Ministry of Health, Labor, and Welfare (MHLW) of neuropsychiatric events in patients receiving either antivirals other than Tamiflu or no antiviral therapy, and 3) analyzing data from the United Kingdom's General Practice Research Database (GPRD). Roche

has also performed additional clinical pharmacology and nonclinical studies to investigate the disposition of Tamiflu in the central nervous system (CNS) and has evaluated potential pharmacological, genetic factors, and drug-drug interactions relating to Tamiflu exposure.

Based upon this body of information, Roche has concluded the following:

- The usage of Tamiflu in pediatric patients is approximately 6 times greater in Japan than in the US.
- There was a substantially higher number of neuropsychiatric events reported in pediatric patients in Japan than in the US in the 2005-2006 and 2006-2007 flu seasons. For pediatric patients, the cumulative reporting rate for neuropsychiatric events per million Tamiflu prescriptions is 99 in Japan and 19 in the US. Thus, taking into account Tamiflu usage, neuropsychiatric events are infrequent events in both countries.
- The early onset of neuropsychiatric events in influenza treatment mirrors the onset of the known systemic symptoms of influenza such as fever, malaise, and myalgia making it difficult to distinguish the effect of the drug from the effects of disease.
- The incidence of neuropsychiatric events in clinical trials and US healthcare claims data suggest no increased risk for neuropsychiatric events with Tamiflu use.
- Neuropsychiatric events similar to those seen with Tamiflu have been reported in patients with influenza who were not taking Tamiflu.
- Clinical pharmacology and nonclinical studies provide no evidence for potential mechanisms for Tamiflu to cause CNS effects.

Roche concludes from the body of all available data that, based on the temporal relationship of the neuropsychiatric adverse events both to influenza and Tamiflu, it is difficult to distinguish between drug and disease. The relative contribution of Tamiflu to the incidence or severity of the neuropsychiatric events seen in influenza patients is unknown. Thus, the information on neuropsychiatric events currently within the Precautions section of the Tamiflu USPI and in the PPI continues to be an accurate assessment of all available updated and expanded data.

2. BACKGROUND ON TAMIFLU

2.1 Description of Product

Tamiflu (oseltamivir phosphate [OP]) is an orally available, ethyl ester pro-drug of oseltamivir carboxylate (OC), which is a potent, stable, and selective inhibitor of influenza A and B neuraminidase. Influenza neuraminidase is important for sustained viral replication in humans and is thought to be involved in preventing influenza virus inactivation. Inhibition of this enzyme by OC is effective for the treatment and prophylaxis of influenza A and B infections.

2.2 Regulatory Background

Tamiflu has been approved in over 80 countries worldwide for both treatment and prophylaxis of influenza. The registration history of Tamiflu in the US is provided in Table 1. In the US, Tamiflu was approved in 1999 for the treatment of uncomplicated acute illness due to influenza infection in adults and adolescents who have been

symptomatic for no more than 2 days. Tamiflu was also approved for the treatment of influenza in children aged 1-12 years and for prophylactic use in persons 13 years of age and older in 2000.

Registration of Tamiflu for the treatment of influenza in children was based on double-blind, randomized, placebo-controlled treatment studies as well as prophylaxis studies in children. Pediatric exclusivity was granted in March 2004 on the basis of the pediatric registration studies and a Phase 3, randomized, open-label study of Tamiflu for the management of influenza in households in which children (aged 1-12 years) participated.

Table 1 Tamiflu US Registration History

Indication	Population	Approval Date
Treatment of influenza	adults	October 27, 1999
Prophylaxis of influenza	adults and adolescents ≥ 13 years of age	November 17, 2000
Treatment of influenza	patients ≥ 1 year of age	December 14, 2000
Pediatric exclusivity	-	March 22, 2004
Prophylaxis of influenza	patients ≥ 1 year of age	December 21, 2005

As required by the BPCA, a routine safety review for Tamiflu was conducted by Roche and FDA during the year following the granting of pediatric exclusivity. This review focused on pediatric deaths and serious adverse events and the results, as required by the BPCA, were presented to the PAC in November 2005. Two clusters of postmarketing reports were identified: serious skin reactions and neuropsychiatric events seen primarily in children in Japan. In response to the postmarketing reports of skin reactions, Roche updated the Precautions section of the USPI and the PPI in December 2005. The consensus of Roche, FDA, and the PAC in November 2005 was that there was insufficient evidence to establish that neuropsychiatric events represented a safety signal for Tamiflu. However, after reviewing reports of neuropsychiatric events in the subsequent flu season, Roche and FDA agreed that it was prudent to be transparent with healthcare professionals about these events and thus, Roche worked with FDA in 2006 to update the Precautions section of the USPI in November 2006 to add the following text:

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 PPI was modified at the same time to add the following text:

People with flu, particularly children, may be at an increased risk of self-injury and confusion shortly after taking TAMIFLU and should be closely monitored for signs and unusual behavior. A healthcare professional should be contacted immediately if the patient taking TAMIFLU shows any signs of unusual behavior.

Since its previous meeting with the PAC, Roche has continued its postmarketing surveillance for neuropsychiatric events associated with Tamiflu and has proactively conducted a number of additional preclinical and clinical studies. The purpose of this document is to update the PAC on Roche's continued pharmacovigilance and due diligence activities for neuropsychiatric events since our previous meeting. The analyses performed are described in Section 3 and the results of these analyses are described in Section 5 through Section 8.

3. OVERVIEW OF CLINICAL DATA SOURCES AND METHODS

Roche has performed an analysis of post-marketing serious neuropsychiatric adverse events reported in children (age ≤ 16 years) for the last two flu seasons to update the PAC. To put into context the postmarketing safety reports, Roche has also performed an analysis by region (US versus Japan) of seasonal Tamiflu usage and has performed several additional analyses to evaluate the potential role of Tamiflu and the potential role of influenza in neuropsychiatric events.

The total numbers of patients and methods used to derive the results for each of these data sources is described in Sections 3.1 to 3.3.3

3.1 Post-marketing Surveillance Data

To identify neuropsychiatric events, prospectively-defined MedDRA high level terms in the System Organ Classes (SOC) of nervous system disorders, psychiatric disorders, and accidents/injuries (reviewed as a possible sequelae of a neuropsychiatric event), that were agreed to with FDA, were used to search the Roche global safety database (this database includes all events reported to Chugai, Roche's marketing partner in Japan). This search involved 51 MedDRA high-level terms and 95 of the associated preferred terms. A database cutoff date of September 15, 2007 was used. Serious neuropsychiatric events were defined as events that resulted in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or were considered clinically significant by the reporter.

To aid in summarization, synonymous preferred terms or terms with similar content were grouped into larger categories; these groupings were guided by ICD-9 schema. For example, the preferred terms, altered state of consciousness, consciousness fluctuating, and depressed level of consciousness were grouped under the category of depressed level of consciousness. The following 13 categories were used:

- Abnormal behavior
- Cognition disturbanc
- Convulsions
- Delirium
- Delusions/perceptual disturbance
- Depressed level of consciousness
- Encephalitis
- Loss of conciousness
- Miscellaneous psychiatric

- Panic attack
- Parasomnia
- Suicidal events
- Accident/injury

The preferred terms associated with each of these categories are listed in Appendix 1.

All pediatric serious neuropsychiatric event cases were medically reviewed and assessed with regard to the following:

- Temporal relationship of Tamiflu use to onset of the neuropsychiatric event
- Temporal relationship of influenza diagnosis to onset of the neuropsychiatric event
- Whether the event occurred during a fever or during defervescence
- Confounding factors such as comedication, medical history, and underlying disease

For these analyses, pediatric patients were defined according to 21CFR 201.57 as patients $\leq$ 16 years of age.

It is important to note that the search for neuropsychiatric events conducted for this update is much broader than the search conducted previously in 2005. The search conducted for neuropsychiatric events in 2005 was based on 35 MedDRA preferred terms compared to the 95 selected preferred terms used in the current categorization. A broader approach was taken to ensure that no events of interest were missed. However, by increasing the sensitivity of the search, specificity was reduced since cases that may/may not be relevant are also retrieved.

It is also important to note the usual limitations associated with postmarketing surveillance data. These include:

1. known under-reporting of events under the voluntary reporting arrangements
2. high variability in documentation and in detail in the submitted reports
3. difficulty in calculating event rates due to limitations in estimating both the numerator and the denominator

Results of the postmarketing surveillance data are presented in Section 5.

3.2 Potential Role of Tamiflu in Neuropsychiatric Events

To evaluate the potential role of Tamiflu in neuropsychiatric events, Roche has evaluated data where a control group exists including pooled pediatric clinical trials and two US healthcare claims databases, MarketScan and United Healthcare (UHC).

3.2.1 Clinical Trials Database

A review of the clinical trials database was conducted to evaluate the types of neuropsychiatric adverse events reported during the conduct of Phase 3 studies in pediatric influenza patients receiving Tamiflu or placebo. This review included all treatment and prophylaxis studies conducted in patients 1 year of age and older, regardless of study design (open label versus placebo controlled) and used the same methodologic approach that was used in the analysis of the postmarketing surveillance data (eg, use of neuropsychiatric event categories).

Results from clinical trials are presented in Section 6.1.

3.2.2 US Claims Databases

As mentioned previously, because the postmarketing surveillance data lack a control group of patients with no antiviral treatment, three retrospective, observational, cohort studies were conducted to compare influenza patients who were or were not treated with Tamiflu in order to assess the potential role of Tamiflu with these events. These studies used data from two US claims databases: MedStat's MarketScan Commercial Claims and Encounters Database and the UHC database. The MarketScan database is comprised of beneficiaries of employer-sponsored health plans and Medicare. The UHC database contains data from patients insured by UHC and from large national employer groups with administrative services provided by UHC.

As the events included in these databases are not assessed as serious or nonserious, all events were included in these analyses.

The objective and methods used for each of these studies, collectively referred to as the claims database studies throughout this document, are described below. Results of the claims database studies are discussed in Section 6.2.

UHC Study

The objective of this study was to identify the incidence of neuropsychiatric events among influenza patients in the UHC database [1]; the study was conducted by i3. Patients ≥ 1 year and ≤ 17 years of age with at least 6 months of plan enrollment and a clinical diagnosis of influenza were identified and then grouped into two propensity score-balanced cohorts: 1) those with a prescription for Tamiflu (60,384 patients) and 2) those with no antiviral treatment (183,786 patients). Patients were followed for 30 days following an influenza diagnosis and medical claims were searched for indications of neuropsychiatric events. The study period ranged from November 1, 1999 through April 30, 2005. Individuals who were hospitalized on the day of diagnosis were omitted from analysis.

Three hierarchical categories of neuropsychiatric outcomes were analyzed: 1) a broad category of any neuropsychiatric event, 2) a more restrictive category of major neuropsychiatric events that excluded chronic disorders, conditions with stated etiology, congenital or hereditary disorders and spinal cord disorders, and 3) a category limited to events specific to CNS stimulation (psychotic reactions, delusion, delirium, confusion, euphoria, hallucination, insomnia, nightmares, night terrors, anxiety, agitation, nervousness, restlessness, irritability, headache, panic states, aggressive behavior, or seizures). Logistic regression was used to compare the risk between cohorts.

MarketScan Study

The objective of the MarketScan Database study was to determine the impact of Tamiflu on the risk of psychiatric events; the study was conducted by Thomson. Psychiatric events were defined as delirium, delusions, psychosis, suicide, and self-inflicted injury [2]. Patients were selected if they received an influenza diagnosis in an outpatient setting during one or more flu seasons (defined as October 1 of one year through March 31 of

the following year) between 2000 and 2006 and had been continuously enrolled in the healthcare program for at least 3 months prior to the influenza diagnosis. Propensity matching was performed to develop a comparable cohort of Tamiflu users (40,704 patients) versus a cohort with no antiviral treatment (40,704 patients). Logistic regression was used to compare the risk between cohorts.

Roche's UHC and MarketScan Study

The third study was conducted by Roche using data from both the MarketScan and the UHC databases. The primary objective of this study was to compare the rate of neuropsychiatric events in pediatric patients who received Tamiflu compared to the rate of neuropsychiatric events in patients, particularly pediatric patients, who did not receive an antiviral medication. Importantly, the study utilized the same methodologic approach that was used in the analysis of the postmarketing surveillance data (ie, the same categories of neuropsychiatric events) with the exception that the accident/injury category was not examined since it would be confounded by events due to other etiologies. Additionally, the same inclusion/exclusion criteria were used in selecting the patient populations from the UHC and MarketScan databases. Inclusion criteria included the presence of a diagnosis of influenza on an outpatient claim and continuous enrollment in the health plan for at least 6 months prior to diagnosis and at least 14 days following diagnosis. Patients who had flu vaccine on the diagnosis date and patients who took other antiviral medications within 3 months of the diagnosis date were excluded. The flu seasons between October 1, 2001 and September 30, 2006 were included. Propensity matching, including matching for a prior history of a neuropsychiatric event, was performed in order to develop comparable cohorts of Tamiflu users and nonusers of antiviral treatments (MarketScan: Tamiflu, 26,287 patients; no antiviral, 26,153 patients; UHC: Tamiflu, 30,196 patients; no antiviral, 30,728 patients). A medical claims search was then conducted for neuropsychiatric adverse events within 14 days following an influenza diagnosis.

3.3 Potential Role of Influenza in Neuropsychiatric Events

To evaluate the potential role of influenza in neuropsychiatric events, Roche has: 1) reviewed literature reports of neuropsychiatric events in influenza patients treated with antivirals other than Tamiflu or no antiviral therapy, 2) reviewed reports to the Japanese MHLW, available on their website, of neuropsychiatric events in patients receiving either antivirals other than Tamiflu or no antiviral therapy, and 3) analyzed data from the GPRD on neuropsychiatric adverse events in influenza patients versus the general GPRD population.

3.3.1 General Practice Research Database

To estimate and compare the incidence of neuropsychiatric events in influenza patients, in particular children, with the rates in the general population, Roche conducted a study using data from the United Kingdom's GPRD. The GPRD is a large longitudinal database of patient's medical records that contains information for 9 million patients. The information recorded in this database includes demographics, outpatient diagnosis, general practitioner consultations, referrals, hospital admissions, and prescriptions. This UK database was selected because the use of Tamiflu is very limited in the UK. Patients

diagnosed with influenza or an influenza-like illness were identified for the flu seasons between 2001 to 2006. A total of 68,771 patients (9,237 pediatric patients [≤ 16 years]) with a diagnosis of influenza or influenza-like illness were identified. Overall, 66,733 patients (97%) had 1 episode of influenza, 1,950 patients (2.8%) had 2 episodes, and 88 patients (0.1%) had 3 or more episodes during the five flu seasons examined. The subset of pediatric patients had a total of 9,472 events of influenza during the five flu seasons. The comparator group was defined as all patients who were alive and active on January 1, 2004 (3,012,203 patients). Patients in both groups were followed for 30 days after diagnosis and the database searched for neuropsychiatric events in the categories of delirium, delusions/perceptual disturbance, panic attack, suicidal events, convulsions, depressed level of consciousness, loss of consciousness, parasomnia, cognition disturbance, and encephalitis. The categories of miscellaneous psychiatric and abnormal behavior that were used in the analysis of postmarketing reports were not used in this analysis because of the nonspecific nature of the preferred terms within each of these categories. The category of accident/injury was also not examined since it would be confounded by events due to other etiologies.

Incidence rates of neuropsychiatric events in the influenza group and in the general population were estimated over 30 days and relative risks computed under the assumption that the observed count of neuropsychiatric events followed a Poisson distribution. Analyses were carried out for all ages together and also separately for pediatric patients (patients ≤ 16 years). Relative risks were adjusted for age, gender, and history of neuropsychiatric events.

Results for the GPRD study are presented in Section 7.1.

3.3.2 Literature Review

The literature was reviewed to identify additional reports of influenza-associated neuropsychiatric events in children regardless of exposure to antiviral treatments. To identify relevant literature reports, Medline and Embase databases were searched for English language publications on July 15th 2007, using a search for any one of the following terms: influenza, influenza A, influenza B, flu, influenza-associated, influenza-like, flu-like, avian flu, and H5N1 along with any one of the following terms: encephalopathy, encephalitis, neuropathy, CNS, psychosis, coma, loss or depressed level of consciousness, unconsciousness, delirium, convulsion, seizures, febrile convulsions, palsy, speech or language disorder, vision disorder, hyperactivity, hypoactivity, lethargy, encephalitis lethargica, hallucination, delusion, EEG changes or abnormalities, neurologic complication, suicide, depression, anxiety, fear, and abnormal behavior. The search identified 338 publications, the abstracts of which were then assessed for either their relevance to oseltamivir or their relevance to influenza-associated neurological disorder. Further references were identified through reading listed citations and from following related links. Five of the identified references were case reports of neuropsychiatric events in influenza patients not receiving Tamiflu. A summary of these case reports is presented in Section 7.2.

3.3.3 MHLW Case Reports of Neuropsychiatric Events with Other Antivirals or No Antiviral Therapy

The Japanese MHLW posts case reports of neuropsychiatric events in influenza patients on their website [3, 4, 5, 6]. Roche reviewed these postings to identify influenza patients treated with antivirals other than Tamiflu or no antiviral treatment with neuropsychiatric events and then categorized the neuropsychiatric events for these patients using the same methodologic approach used in the analysis of postmarketing surveillance data. MHLW reports of neuropsychiatric events for patients taking Tamiflu are present in the Roche global drug safety database and were included in the analysis of postmarketing reports.

Results for the MHLW case reports are presented in Section 7.3.

4. TAMIFLU USAGE

Since first approval, approximately 48 million patients, the majority (75%) of whom are located in Japan, have received a prescription for oseltamivir (Appendix 2). The number of Tamiflu prescriptions for pediatric patients was higher in Japan than in the US and the Rest of World during the 2005-2006 and 2006-2007 influenza seasons (Figure 1). Total cumulative usage of Tamiflu from approval through the 2007 influenza season in pediatric patients is 17.6 million prescriptions in Japan, 2.9 million prescriptions in the US, and 0.23 million prescriptions in the Rest of World.

Higher Tamiflu usage in Japan is a reflection of the clinical management practices for influenza in this country. In 1994, the Japanese government discontinued the mass annual influenza vaccination program for Japanese pediatric patients (children aged < 19 years) amid concerns about the efficacy of the program in suppressing epidemics. Following termination of the program, a steep rise was noted in the number of pediatric patients with influenza and influenza-associated acute encephalopathy/encephalitis [7]. As a result of these findings, vaccination rates have subsequently increased in Japan. In 2005, there were 303 doses of vaccine distributed per 1,000 population compared with 10 doses per 1,000 population in the 1997. Vaccine usage in Japan in 2005 was similar to that in the US (274 doses per 1,000 population) [8]. In 2006, 28% of the Japanese population received an influenza vaccination. The rates of vaccination were highest in the very young (51.5% of children aged 1-6 years; 36.9% in children aged > 6-13 years) and in those over 65 years of age (51.1%). Adolescents over 13 years of age and adults < 65 years of age had the lowest rate of vaccination [9].

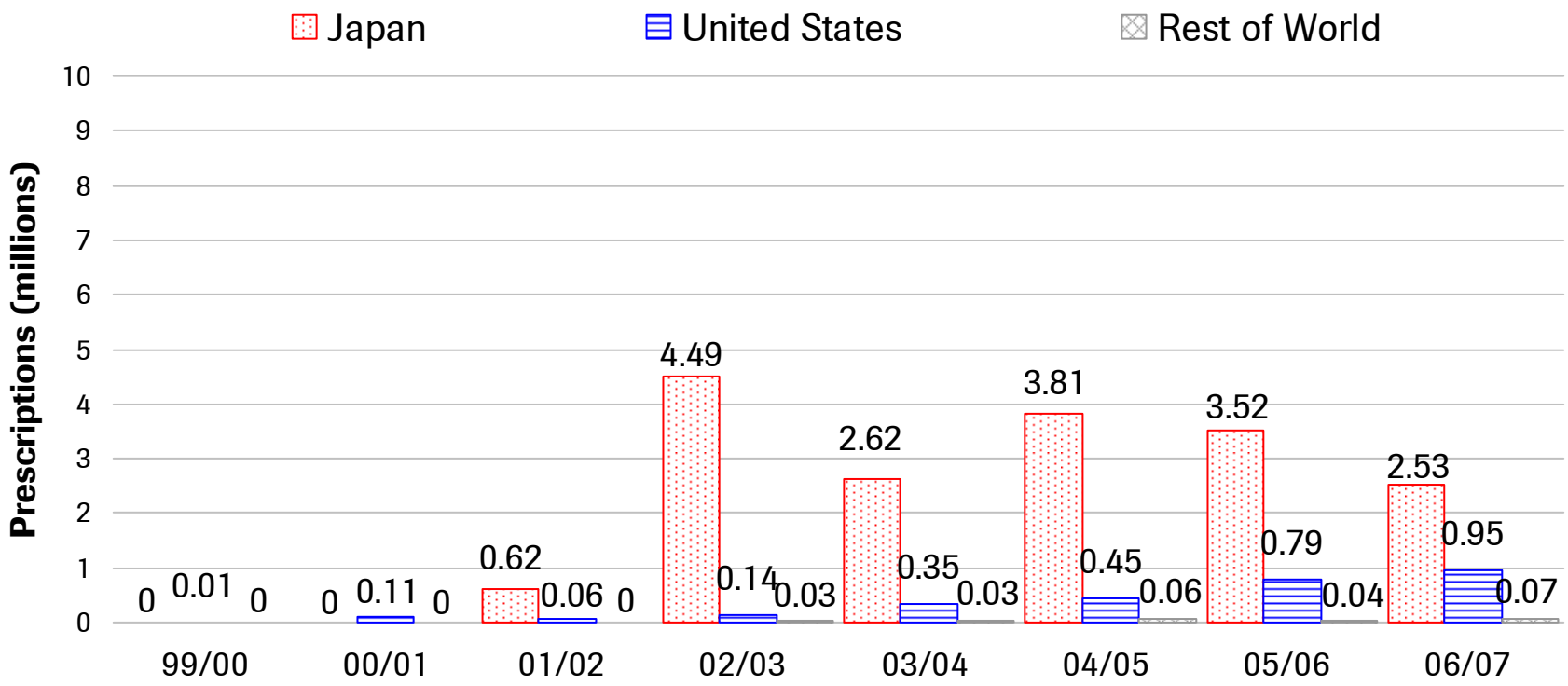
There are some additional differences in the clinical management of influenza between the US and Japan. These include the following:

- Physician consultation occurs early in the course of illness with 91% of the patients who consult a physician doing so within the first 48 hours [9].
- Unlike most other countries, the use of point-of-care diagnostic testing for influenza is a standard, reimbursable medical practice in Japan. Almost all Japanese patients who present with influenza-like illness receive a rapid test for influenza [10].
- Antiviral treatments for influenza are fully reimbursed in Japan. Based upon influenza surveillance data and IMS prescription data in Japan, it is estimated that

approximately 50% of Japanese patients with confirmed influenza received Tamiflu treatment in 2004 [10].

- Japanese guidelines for the management of influenza patients with encephalitis/encephalopathy recommend Tamiflu [11].

Figure 1 **Tamiflu Prescriptions by Season and Region: Pediatric Usage**



5. NEUROPSYCHIATRIC EVENTS IN POSTMARKETING SURVEILLANCE

5.1.1 Tamiflu Treatment of Influenza

The total cumulative number of pediatric patients with neuropsychiatric events (both serious and nonserious) is higher in Japan than in the US (Table 2). Since approval of the pediatric indication, the overall crude reporting rate for neuropsychiatric events is 19 neuropsychiatric events per million prescriptions written in the US and 99 neuropsychiatric events per million prescriptions written in Japan suggesting that neuropsychiatric events are infrequent events in both countries.

Table 2 Cumulative Reporting Rate of Neuropsychiatric Events in Pediatric Patients Per Million Tamiflu Prescriptions Written

Region	Patients with NPAEs	Total Rx (Millions)	Overall Reporting Rate (NPAEs/1,000,000 Rx Written)
US	55	2.85	19
Japan	1745	17.59	99
Rest of World	8	0.23	35

NPAEs = neuropsychiatric events

There was a marked increase in the reporting of pediatric neuropsychiatric events (both serious and nonserious) in the 2005-2006 and 2006-2007 flu seasons (Figure 2 and Figure 3). During these seasons, there was no increase in the incidence of influenza. In addition, there were no changes to drug manufacturing, formulation, dosage or administration of Tamiflu in Japan during these seasons. In the absence of any obvious explanation for the increased adverse event reporting, Roche explored other factors which may have influenced reporting rates over these two influenza seasons. One notable factor was an increase in physician and consumer awareness of such events as a result of both media reports and communications to healthcare professionals. During the period of 2005 to mid-2007, there was an increase in Japanese media reports. In addition, physician awareness was also increased during this time period as a result of the following: 1) a Japanese MHLW request for reports of neuropsychiatric events in both treated and untreated influenza patients posted on its website, 2) two "Dear Healthcare Professional" letters issued in February and March 2007, and 3) labeling restriction for Tamiflu in Japan in patients aged 10-19 years in March 2007. This increased awareness may have lowered the threshold at which point a healthcare provider or caregiver decides to voluntarily report an adverse event.

The review of serious neuropsychiatric events reported over the last two flu seasons revealed the following:

- The majority of the serious events (67%) occurred within 2 days of the diagnosis of influenza.
- 80% of the events occurred within 2 days of the start of Tamiflu treatment.
- Fever was present at the onset of the event in up to 44% of children.
- More events occurred in males than in females (ratio of approximately 2:1).
- Most events (52%) occurred in patients aged 6 to 12 years.

- Most events (87%) either improved or resolved.

The most frequently reported serious neuropsychiatric events in Japan during the 2005-2006 and 2006-2007 influenza seasons were in the following categories: abnormal behavior (140 patients), convulsions (52 patients), delusions/perceptual disturbances (41 patients), and delirium (30 patients) (Table 3). The most frequently reported serious neuropsychiatric events in the US during the 2005-2006 and 2006-2007 influenza seasons were in the following categories: convulsions (8 patients), delirium (5 patients), and delusions/perceptual disturbances (5 patients) (Table 3).

A small number (7 patients: 6 males and 1 female) of accidents/injuries, predominantly falls, occurred in pediatric patients in both influenza seasons. All of the accidents/injuries were reported in Japan. Five of the accidents/injuries were associated with neuropsychiatric events and three of these accidents were fatal (see Section 5.1.3 for further discussion).

Figure 2 **Seasonal Reporting Rate of All Neuropsychiatric Events in Pediatric Patients per Million Prescriptions Written**

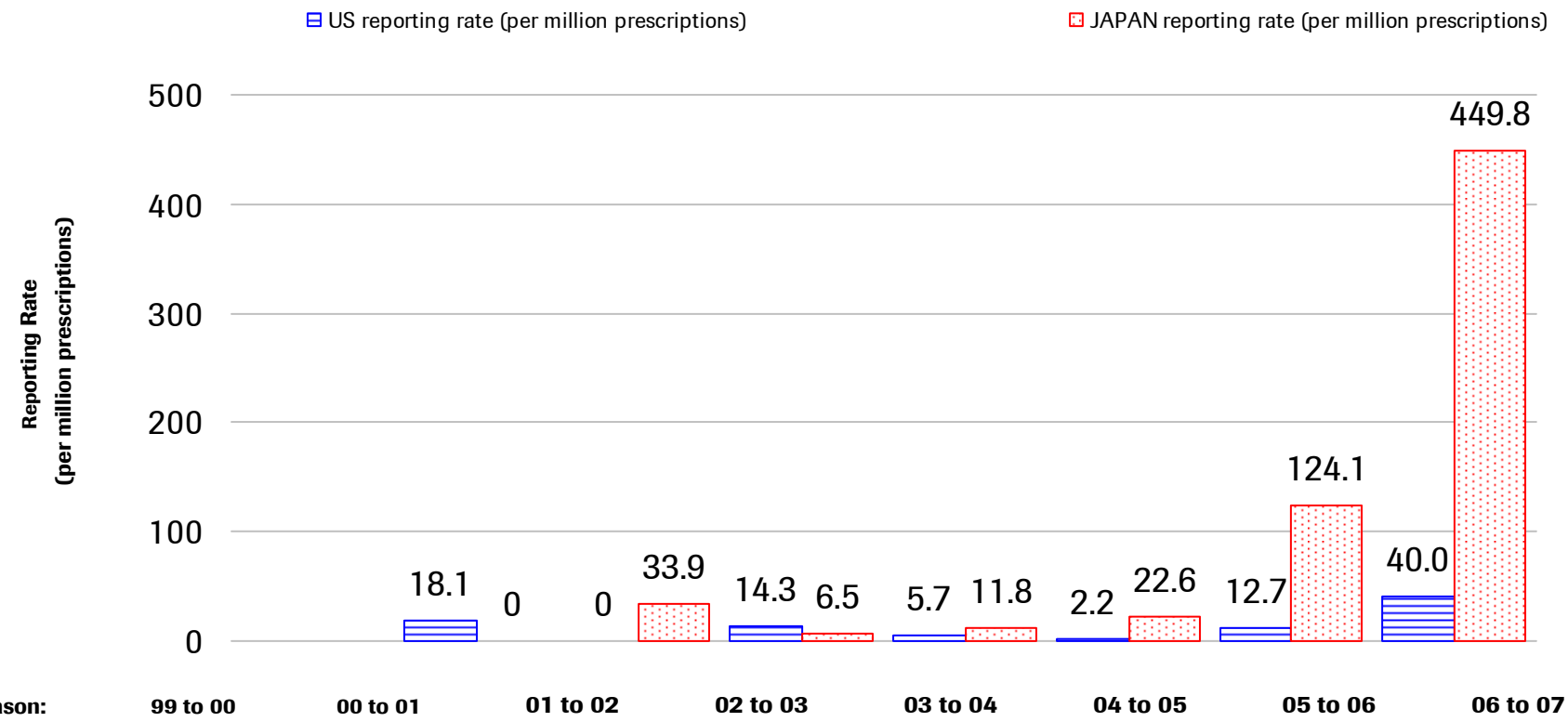


Figure 3 **Seasonal Reporting Rate of Serious Neuropsychiatric Events in Pediatric Patients**

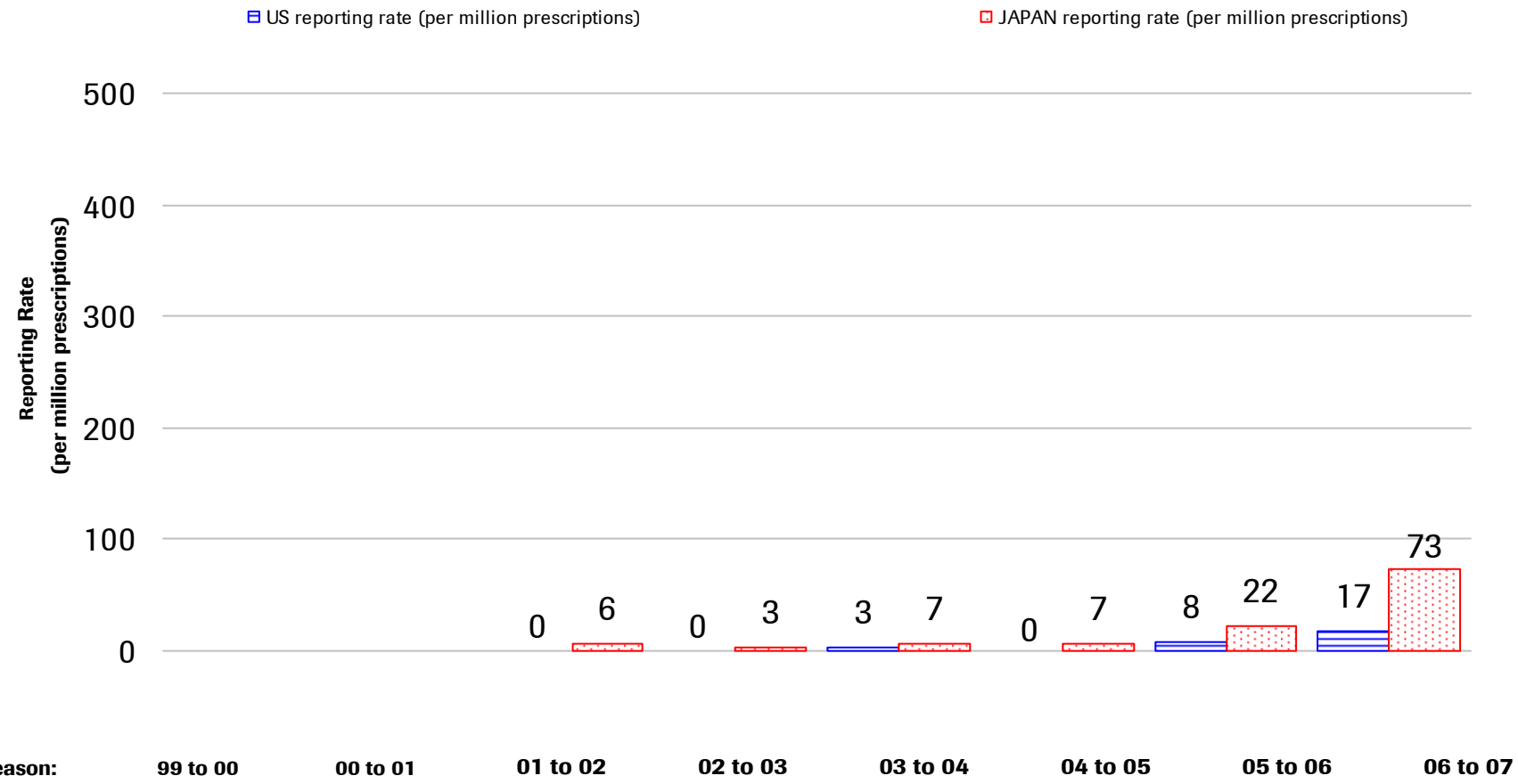


Table 3 Number of Patients with Serious Pediatric Neuropsychiatric Events – Tamiflu Treatment

NPAE Category[1]	US		Japan	
	05-06	06-07	05-06	06-07
Abnormal behavior	0	2	35	105
Accidental injury	0	0	2	5
Cognition disturbance	0	1	2	2
Delirium	0	5	15	15
Delusions/perceptual disturbance	1	4	17	24
Decreased level of consciousness	0	0	11	17
Parasomnia	0	0	0	3
Convulsions	4	4	13	39
Encephalitis	0	1	0	1
Loss of consciousness	0	1	0	6
Miscellaneous psychiatric	1	2	8	11
Panic attack	0	1	0	0
Suicidal events	0	0	0	2

[1]Categorized by ICD-9 schema

5.1.2 Tamiflu Prophylaxis of Influenza

Six children were reported in the postmarketing surveillance database to have received Tamiflu for influenza prophylaxis and to have had a neuropsychiatric event (3 serious and 3 nonserious) (Table 4). All of these cases had confounding factors associated with the neuropsychiatric event that may likely have been the cause of these events. In one patient, signs of the neuropsychiatric event (agitation) were present before the start of Tamiflu. Three of the children had symptoms consistent with influenza (eg, pyrexia) and thus, cannot be considered true prophlaxis cases. Two children had confounding medical conditions (loss of consciousness secondary to orthostatic hypotension; bacterial encephalitis in a child with acute myeloid leukemia).

Table 4 Pediatric Neuropsychiatric Events – Influenza Prophylaxis[1]

Patient	NPAE	Comment
14 yr old female; Japan	Delirium*	Pyrexia present at onset of delirium; influenza diagnosed shortly after the start of Tamiflu
4 yr old female; Japan	Convulsion*	Pre-existing febrile convulsion; pyrexia at onset of convulsion – consistent with influenza infection
10 yr old female; US	Loss of consciousness	Orthostatic hypotension associated with syncope, rash, swollen fingers
1 yr old male, Japan	Agitation	Excitement present before the start of Tamiflu
6 yr old male; Japan	Encephalitis*	Concurrent conditions included acute myeloid leukemia, sepsis, and bacterial encephalitis
15 yr old male; Japan	Abnormal behavior	Agitation and pyrexia (consistent with influenza infection) also present

[1]Several neuropsychiatric events, including psychotic disorder*, delusion*, hallucination, agitation, anxiety, depression, and disorientation, were reported in a 17-year-old male in the US. All events persisted for at least 6 months. No additional follow-up information is currently available.
*Serious adverse event

5.1.3 Deaths Associated with Neuropsychiatric Events

Four deaths were reported in pediatric patients who had either a neuropsychiatric event or accident/injury during the 2005-2006 and 2006-2007 influenza seasons. All deaths were in Japan. Deaths were due to falls in 3 patients (MCNs 483425, 453977, and 484906) and encephalitis in 1 patient (MCN 490664). None of the deaths due to falls were considered suicides. Two of the patients with fatal falls (MCNs 403186 and 484906) had an additional neuropsychiatric event reported (depressed level of consciousness and abnormal behavior, respectively).

Two deaths (MCNs 372431 and 397263) were reported in patients aged 17 to 21 years: one due to accident/injury (17-year-old, Japanese male) and one due to encephalitis (19-year-old, Japanese female).

5.1.4 Summary

There was a marked continued increase in the reporting of neuropsychiatric events from Japan and the US during the 2005-2006 and 2006-2007 influenza seasons; this increase was greater in Japan than in the US. For pediatric patients, the cumulative reporting rate for neuropsychiatric events per million Tamiflu prescriptions is 99 in Japan and 19 in the US. Thus, taking into account Tamiflu usage, neuropsychiatric events are infrequent events in both countries.

The neuropsychiatric event rate was higher in Japan than in the US and more events were seen in males than in females (2:1 ratio). Most events occurred in patients aged 6 to 12 years. Neuropsychiatric events were typically seen early after the onset of influenza and in the presence of fever making it difficult to distinguish between drug and disease.

The most frequently reported serious neuropsychiatric events in Japan during the 2005-2006 and 2006-2007 influenza seasons were in the following categories: abnormal behavior (140 patients), convulsions (52 patients), delusions/perceptual disturbances (41 patients), and delirium (30 patients) (Table 3). The most frequently reported serious neuropsychiatric events in the US during the 2005-2006 and 2006-2007 influenza seasons were in the following categories: convulsions (8 patients), delirium (5 patients), and delusions/perceptual disturbances (5 patients).

6. POTENTIAL ROLE OF TAMIFLU IN NEUROPSYCHIATRIC EVENTS

To evaluate the potential role of Tamiflu in neuropsychiatric events, Roche has evaluated data that provides a comparative control group: 1) its pooled clinical trials, and 2) two US healthcare claims databases, MarketScan and UHC.

6.1 Clinical Trials

In clinical studies, neuropsychiatric events in pediatric patients were only seen in the treatment studies (Tamiflu, 1,080 patients; placebo, 738 patients); no events were seen in the prophylaxis studies (Tamiflu, 49 patients; no placebo patients). In the treatment studies, 3 patients (< 1%) in the Tamiflu group and 2 patients (< 1%) in the placebo group had events in the miscellaneous psychiatric category. These events included anxiety (Tamiflu, 1 patient; placebo, 1 patient) and irritability (Tamiflu, 2 patients; placebo, 1 patient). No events were reported in the other neuropsychiatric event categories.

6.2 Claims Database Studies

Based on the adjusted odds ratio, the use of Tamiflu was not associated with an increased risk in pediatric patients for any of the three groupings of neuropsychiatric events examined in the UHC study (Table 5). The use of Tamiflu was also not associated with an increased risk for the psychiatric events examined in the MarketScan Study (Table 6) or for an increased risk of any of the neuropsychiatric adverse event categories in Roche's study of the UHC and MarketScan databases (Table 7 and Table 8).

Table 5 Odds Ratios and 95% Confidence Intervals for Neuropsychiatric Events in Pediatric Patients[1] - UHC Database

Event	Tamiflu N=20,501 N (%)	No Antivirals N=84,871 N (%)	Adjusted Odds Ratio	95% Confidence Interval
Any neuropsychiatric event	251 (1.22)	1,032 (1.22)	0.96	0.83, 1.12
Major neuropsychiatric events	224 (1.09)	878 (1.03)	1.00	0.85, 1.18
CNS stimulations	157 (0.77)	605 (0.71)	1.03	0.85, 1.25

[1]Pediatric patients were defined as patients ≤17 years of age

Table 6 Odds Ratios and 95% Confidence Intervals for Psychiatric Events[1] – MarketScan Database

Age Group	Tamiflu Users N=14,214 N (%)	No Antivirals N=14,220 N (%)	Adjusted Odds Ratio	95% Confidence Interval
All pediatric	72 (0.5)	113 (0.8)	0.67	0.5, 0.93
< 1 year	0	0	-	-
1-2 years	0	0	-	-
3-5 years	2 (0.1)	6 (0.3)	0.34	0.07, 1.70
6-12 years	29 (0.5)	45 (0.8)	0.67	0.4, 1.12
13-17 years	41 (0.9)	62 (1.3)	0.66	0.43, 1.02

[1]Includes delirium, delusion, psychosis, suicide, and self-inflicted injury

Table 7 Neuropsychiatric Events in Pediatric Patients[1]: Roche's UHC Database Study

Event	Tamiflu N=30,196 N (%)	No antivirals N=30,728 N (%)	Odds Ratio	95% Confidence Interval
Any neuropsychiatric event	118 (0.38)	138 (0.45)	0.85	0.66, 1.09
Delirium	0	1 (<0.1)	-	-
Delusions/perceptual disturbances	4 (0.01)	5 (0.02)	0.80	0.21, 2.96
Panic attack	0	1 (<0.1)	-	-
Suicidal events	2 (0.01)	0	-	-
Convulsion	70 (0.23)	76 (0.25)	0.92	0.66, 1.27
Depressed level of consciousness	2 (0.01)	4 (0.01)	0.50	0.09, 2.71
Loss of consciousness	23 (0.07)	21 (0.07)	1.09	0.60, 1.97
Parasomnia	1 (<0.1)	3 (0.01)	0.33	0.03, 3.19
Cognition disturbance	0	1 (<0.1)	-	-
Abnormal behavior	0	0	-	-
Encephalitis	7 (0.02)	17 (0.06)	0.41	0.17, 0.99
Miscellaneous psychiatric	13 (0.04)	19 (0.06)	0.68	0.34, 1.38

[1]Pediatric patients were defined as patients ≤ 16 years of age

Table 8 Neuropsychiatric Events in Pediatric Patients[1]: Roche's MarketScan Database Study

Event	Tamiflu N=26,287 N (%)	No antiviral N=26,153 N (%)	Odds Ratio	95% Confidence Interval
Any neuropsychiatric event	50 (0.19)	63 (0.24)	0.79	0.54, 1.14
Delirium	0	0	-	-
Delusions/perceptual disturbances	2 (0.01)	1 (<0.1)	1.99	0.18, 21.95
Panic attack	0	1 (<0.1)	-	-
Suicidal events	0	0	-	-
Convulsion	27 (0.10)	41 (0.16)	0.65	0.40, 1.06
Depressed level of consciousness	2 (0.01)	1 (<0.1)	1.99	0.18, 21.95
Loss of consciousness	9 (0.03)	11 (0.04)	0.81	0.34, 1.96
Parasomnia	0	0	-	-
Cognition disturbance	1 (<0.1)	1 (<0.1)	0.99	0.06, 15.91
Abnormal behavior	0	0	-	-
Encephalitis	2 (0.01)	3 (0.01)	0.66	0.11, 3.97
Miscellaneous psychiatric	8 (0.03)	7 (0.03)	1.14	0.41, 3.14

[1]Pediatric patients were defined as patients ≤ 16 years of age

6.3 Summary

Clinical trials data show no increase in neuropsychiatric events for Tamiflu-treated patients compared to patients treated with no antivirals. Data from the claims database studies indicate no increased risk for neuropsychiatric events with Tamiflu use.

7. POTENTIAL ROLE OF INFLUENZA IN NEUROPSYCHIATRIC EVENTS

To evaluate the potential role of influenza in neuropsychiatric events, Roche has: 1) analyzed data from the GPRD medical database, 2) reviewed literature reports of neuropsychiatric events in influenza patients treated with antivirals other than Tamiflu or no antiviral therapy, and 3) reviewed reports to the Japanese MHLW of neuropsychiatric events in patients receiving either antivirals other than Tamiflu or no antiviral therapy.

7.1 General Practice Research Database

Within the overall GPRD population (pediatric and adult patients), there was a statistically significant increased risk (2 to 2.5-fold) for any neuropsychiatric event, delusions, panic attack, depressed level of consciousness, loss of consciousness, and cognition disturbances in patients with influenza compared to patients in the general GPRD population (Table 9).

The incidence of neuropsychiatric events in pediatric patients was low in both patients with influenza and the general GPRD population (Table 10). The small number of

pediatric influenza patients did not allow for robust estimates of the relative risk of neuropsychiatric events in the pediatric population.

A total of 56 influenza patients (7 pediatric patients) in the GPRD database had Tamiflu treatment. None of these patients had a neuropsychiatric event.

Table 9 Incidence of Neuropsychiatric Events in the GPRD Database – All Patients

Event	Influenza Patients N=68,771		General GPRD Population N=3,012,203		Adjusted[3] Relative Risk (95% CI)	p-value
	Number	Rate per 100 pt months	Number	Rate per 100 pt months		
Any neuropsychiatric event	258	0.36	5474	0.18	1.75 (1.54-1.98)	<0.0001
Delirium	0	0	4	0.0001	0	0.9
Delusions/perceptual disturbances	13	0.02	283	0.009	1.83 (1.05-3.19)	0.03
Panic attack	65	0.09	1067	0.04	1.85 (1.44-2.38)	<0.0001
Suicidal events (narrow)[1]	2	0.003	76	0.003	0.93 (0.23-3.9)	0.97
Suicidal events (wide)[2]	7	0.01	194	0.006	1.27 (0.60-2.71)	0.52
Convulsions	45	0.06	1439	0.05	1.26 (0.93-1.69)	0.13
Depressed level of consciousness	10	0.014	178	0.006	2.5 (1.29-4.64)	0.005
Loss of consciousness	57	0.08	1006	0.03	2.3 (1.8-2.98)	<0.0001
Parasomnia	2	0.003	119	0.004	0.7 (0.20-2.9)	0.6
Cognition disturbance	65	0.09	1258	0.04	2.4 (1.85-3.05)	<0.0001
Encephalitis	1	0.001	9	0.0003	2.9 (0.35-24.5)	0.3

[1]Suicide (narrow) includes only those terms that mentioned suicide (not necessarily completed).
[2]Suicide (wide) includes, in addition to suicide (narrow), intentional or deliberate poisoning, overdose, or injury (without mention of suicide)
[3]Relative Risks adjusted for age, gender and history of neuropsychiatric events.

Table 10 Incidence of Neuropsychiatric Events in the GPRD Database –Pediatric Patients

Event	Influenza Patients N=9,237		General GPRD Population N=533,274	
	Number	Rate per 100 pt months	Number	Rate per 100 pt months
Delirium	0	0	0	-
Delusions/perceptual disturbances	0	0	2	0.0004
Panic attack	1	0.01	23	0.0043
Suicidal events (narrow)[1]	0	0	0	0
Suicidal events (wide)[2]	0	0	13	0.0024
Convulsions	8	0.08	215	0.0403
Depressed level of consciousness	0	0	9	0.0017
Loss of consciousness	3	0.03	93	0.0174
Parasomnia	0	0	39	0.0073
Cognition disturbance	0	0	6	0.0011
Encephalitis	0	0	2	0.0004

[1]Suicide (narrow) includes only those terms that mentioned suicide (not necessarily completed).
[2]Suicide (wide) includes, in addition to suicide (narrow), intentional or deliberate poisoning, overdose, or injury (without mention of suicide)

7.2 Literature Reports of Neuropsychiatric Events

Five literature reports of pediatric case series in a small number of patients were identified that compared neuropsychiatric events associated with influenza, including delirious behavior, abnormal behavior, confusion, visual, auditory and olfactory hallucinations, encephalitis, and seizure [12, 13, 14, 15, 16]. Two of the case series involved Japanese children and three involved Taiwanese children.

Neuropsychiatric events were seen to occur in both Japanese and Taiwanese children with influenza who received antivirals other than Tamiflu and those with no antiviral treatment. The events occurred predominantly in males and early in the course of illness. A temporal association with fever was noted in one case series.

There was no difference in the nature or timing of neuropsychiatric events in children who received Tamiflu versus those who did not.

7.3 MHLW Case Reports of Neuropsychiatric Events with Other Antivirals or No Antiviral Therapy

As of June 16, 2007, there were 5 case reports of neuropsychiatric events on amantidine, 12 case reports of neuropsychiatric events on zanamivir, and 25 case reports of neuropsychiatric events in the absence of antiviral therapy posted on the MHLW website (Table 11). The type and severity of the neuropsychiatric events reported in influenza

patients on other antivirals or no antiviral therapy were similar to the events seen in some of the Tamiflu postmarketing surveillance cases including cases of delirium with a prominent behavioral abnormality including death. More cases were reported in males than in females (2:1 ratio) and cases were predominantly in children (Table 12). A sampling of the narratives of these cases, including a few for the Tamiflu cases posted on the MHLW website (analyzed in postmarketing surveillance), is provided in Appendix 5.

Table 11 Neuropsychiatric Case Reports to the MHLW

Neuropsychiatric Event Category	Amantidine N=5	Zanamivir N=12	No antivirals N=25
Abnormal behavior	2	10	10
Accidental injury	0	0	2
Cognition disturbance	4	1	0
Delirium	0	1	4
Delusions/perceptual disturbance	1	2	2
Depressed level of consciousness	1	0	1
Suicidal events	1	1	0
Miscellaneous psychiatric	2	2	1
Parasomnia	0	0	1
Suicidal events	0	1	0
Death	1	0	1

Table 12 Patient Demographics for Neuropsychiatric Case Reports to the MHLW

Treatment	Males/Females	< 20 years	≥ 20 years
Amantidine (N=6)	3/2	3	2
Zanamivir (N=12)	8/4	11	1
No antiviral (N=25)	18/7	24	1

7.4 Summary

Data from the GPRD suggests an increased risk for certain neuropsychiatric events in influenza patients compared to the general population. Review of data from the literature and the MHLW website show that neuropsychiatric events, similar to those observed with Tamiflu treatment, occur in patients who do not receive antiviral treatment or who receive antivirals other than Tamiflu.

8. Exploration of Potential Pharmacological Mechanisms for Neuropsychiatric Adverse Events

Neuropsychiatric events were not observed in any of the preclinical studies conducted for Tamiflu registration. However, to explore whether or not there is a possible previously unidentified pharmacological mechanism for the neuropsychiatric adverse events

observed in Japan, Roche has conducted or is conducting a series of additional clinical and preclinical studies. Possible pharmacological mechanisms explored in these studies include the following: 1) systemic clinical pharmacokinetics, 2) CNS penetration, 3) human neuraminidase and receptor targets, and 4) pharmacogenetic or drug-drug interaction targets related to exposure.

The results of these investigations and other relevant studies from the Tamiflu development program are described below.

8.1 Systemic Clinical Pharmacokinetics

Studies that had been conducted during the Tamiflu development program enabled comparison of the exposure of the prodrug of Tamiflu, OP, and its metabolite, OC, in Japanese and Caucasian adults and children [17, 18].

No differences in the PK of either OP or OC were seen between Japanese and Caucasian adults or children (Appendix 3 and Appendix 4).

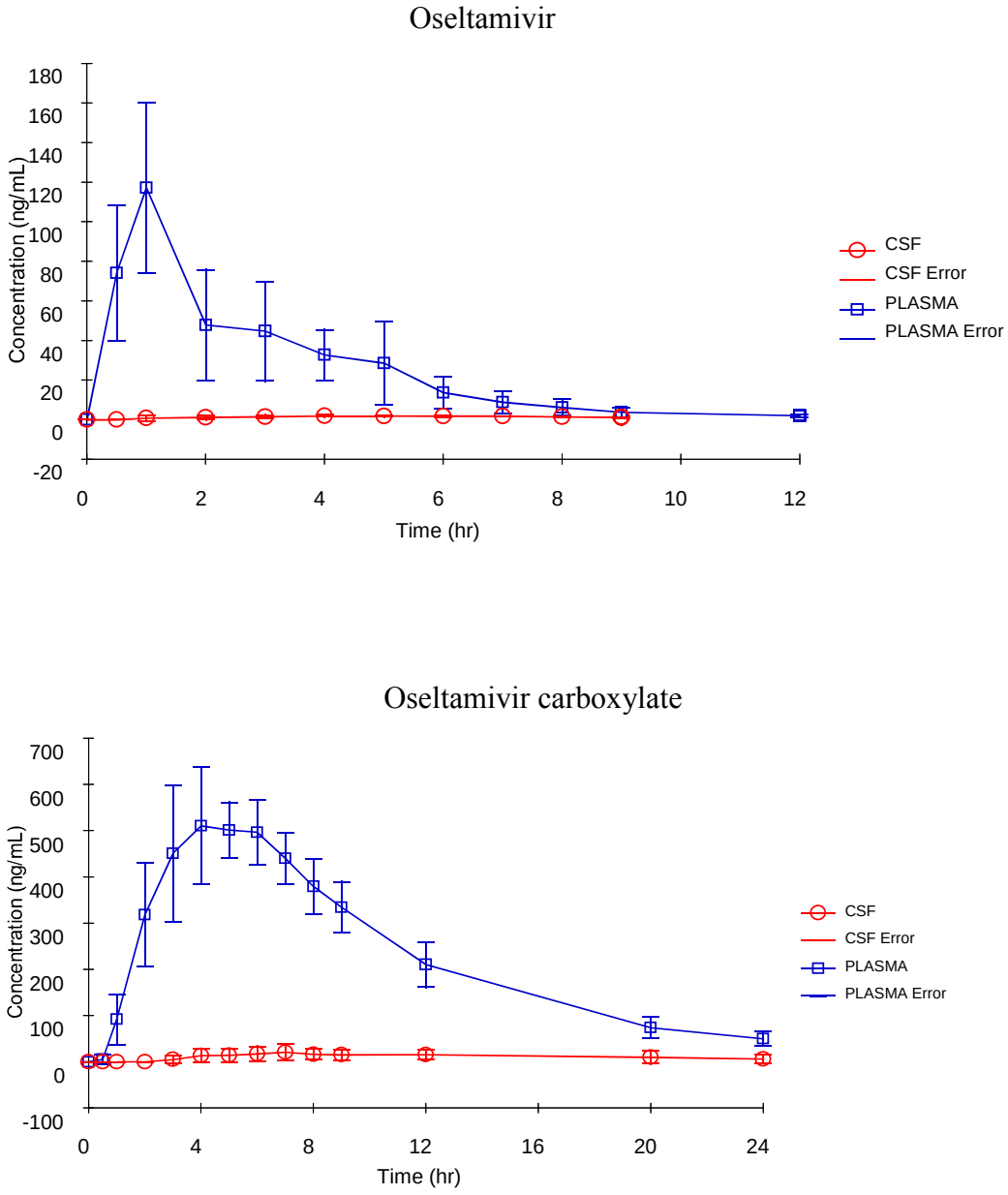
8.2 CNS Penetration

For Tamiflu to have a direct role in the genesis of neuropsychiatric events, it must be able to enter the CNS in sufficient concentrations to exhibit pharmacological effects, as discussed in Section 8.3. To investigate the penetration of OP and OC in the CNS, Roche conducted a single-dose study that investigated the concentration of OC and OP in cerebrospinal fluid (CSF) after oral administration of a single 150 mg dose of Tamiflu to 8 healthy volunteers (4 of Japanese origin and 4 Caucasians). CSF was shown to be a marker for CNS penetration after a preclinical study in adult rats demonstrated that CSF levels of OP and OC are similar to brain concentrations.

Limited CNS penetration was seen for both OP and OC in Japanese and Caucasian subjects in the presence of similar detectable plasma levels for both groups (Figure 4). The AUC CSF/plasma ratios for the total population for OP and OC were 2.33 ± 1.06% and 2.73 ± 3.78%, respectively.

These data suggest that the extent of CNS exposure to either OP or OC at therapeutically relevant doses is limited.

Figure 4 Plasma and CSF Concentrations of OP and OC in Healthy Volunteers (4 Japanese and 4 Caucasian Subjects)



8.3 Receptor Studies

Roche has also conducted studies to assess whether or not OP or OC has pharmacological activity against human neuraminidase in addition to viral neuraminidase or activity against other receptors or ion channels relevant for CNS activity and overall safety.

Neither OP nor OC exhibited inhibitory activity against rat or monkey CNS neuraminidase at concentrations up to 1 mM. In addition, neither OP nor OC, at concentrations up to and including 30 µM (approximately 30 and 100-fold of the OC and OP therapeutic plasma Cmax values, respectively), showed any stimulatory or inhibitory

activity against a panel of 155 different, mostly human targets including those of known relevance for emotion and behavior such as dopamine and NMDA receptors.

As CSF concentrations approximate 3% of the plasma levels of OP and OC (Section 8.2), the above margins based on plasma levels are considered highly conservative.

8.4 Pharmacogenetic and Drug-Drug Interaction Targets Relating to Tamiflu Exposure

Although no significant differences were seen between Japanese and Caucasian subjects in systemic PK in either adults or children, Roche has evaluated whether or not genetic variation or drug-drug interactions could possibly contribute to variability in Tamiflu exposure in some individuals.

There are three well-defined pathways that contribute to the metabolism/distribution of Tamiflu where genetic variation could lead to differences in systemic or CNS exposure of either OP or OC. Roche has explored the theoretical consequences of complete inhibition of each of these pathways due to underlying genetic variation and concluded that the predicted levels of OP and OC are within the established safety margins if each of these pathways are individually inhibited (Table 13). Thus, genetic polymorphisms that affect the systemic or CNS pharmacokinetics of OP or OC do not offer a plausible mechanism for neuropsychiatric adverse events.

An assessment of the pediatric neuropsychiatric event cases was also performed to determine whether or not there was evidence for a drug-drug interaction that could disrupt any of these three pathways. This assessment involved a direct evaluation of all concomitant medications among children ≤ 16 years with serious neuropsychiatric events and showed no evidence for a drug interaction underlying the neuropsychiatric adverse events reported.

Table 13 Molecular Sites of Potential Genetic Variation and the Consequence of Inhibition on Tamiflu Pharmacokinetics

Pathway	Consequence of Inhibition
Conversion of OP to the active metabolite OC via carboxylesterase 1 (CES1)	Predicted levels of OP would be within the range of exposures observed in clinical studies without neuropsychiatric adverse events
Renal tubular secretion of OC via organic anion transporter 1 (OAT1)	OC is a weak substrate of OAT1. If inhibited by probenecid, OC levels increase 2.5-fold which is well within the exposure seen in clinical studies
Transport of OC out of the brain by OAT1	OAT1's role in brain transport considered of low clinical relevance
Transport of OP out of the brain by p-glycoprotein (P-gp)	Predicted brain levels of OP are within established safety margins in the absence of P-gp export

8.5 Summary

Clinical and nonclinical studies provide no evidence for potential mechanisms for Tamiflu to cause CNS effects. Additional studies are ongoing and the results will be provided to the FDA as soon as available.

9. CONCLUSIONS

Based on a comprehensive evaluation of available clinical and preclinical data, Roche has concluded the following:

- The usage of Tamiflu in pediatric patients is approximately 6 times greater in Japan than in the US.
- There was a substantially higher number of neuropsychiatric events reported in pediatric patients in Japan than in the US in the 2005-2006 and 2006-2007 flu seasons. For pediatric patients, the cumulative reporting rate for neuropsychiatric events per million Tamiflu prescriptions is 99 in Japan and 19 in the US. Thus, taking into account Tamiflu usage, neuropsychiatric events are infrequent events in both countries.
- The early onset of neuropsychiatric events in influenza treatment mirrors the onset of the known systemic symptoms of influenza such as fever, malaise, and myalgia making it difficult to distinguish the effect of the drug from the effects of disease.
- The incidence of neuropsychiatric events in clinical trials and US healthcare claims data indicate no increased risk for neuropsychiatric events with Tamiflu use.
- Neuropsychiatric events similar to those seen with Tamiflu have been reported in patients with influenza who were not taking Tamiflu.
- Clinical pharmacology and nonclinical studies provide no evidence for potential mechanisms for Tamiflu to cause CNS effects.

Roche concludes from the body of all available data that, based on the temporal relationship of the neuropsychiatric adverse events both to influenza and Tamiflu, it is difficult to distinguish between drug and disease. The relative contribution of Tamiflu to the incidence or severity of the neuropsychiatric adverse events seen in influenza patients is unknown. Thus, the information on neuropsychiatric events currently within the Precautions section of the Tamiflu USPI and in the PPI continues to be an accurate assessment of all available updated and expanded data.

10. FUTURE ACTIVITIES

Roche has a number of ongoing preclinical and clinical studies that will continue to explore whether or not there is a pharmacological mechanism for neuropsychiatric events. These studies are outlined in Table 14.

Roche will continue to monitor the occurrence of neuropsychiatric events in the postmarketing setting. An additional retrospective, observational cohort study using data from the Kaiser Permanente database will also be initiated to compare the incidence rates of neuropsychiatric events following: 1) a clinical diagnosis of influenza, 2) laboratory-confirmed influenza, and 3) Tamiflu treatment versus no antiviral treatment.

Table 14 Ongoing Preclinical and Clinical Studies of Tamiflu CNS Disposition and CNS Activity

Experimental Objective	Study
Can OP be converted to OC in the brain?	• In vitro functional study using human brain tissue • Rat study with intracerebroventricular administration of Tamiflu to assess conversion of OP to OC via brain carboxylesterase
Does OP have the potential for CNS activity?	• In vitro functional activity assay using human neuraminidases 1-4 expressed in a cell-based system • Juvenile rat toxicology study assessing behavior, histopathology, and brain penetration of OP and OC following oral administration of Tamiflu • Adult rat toxicology study assessing behavior, histopathology, and brain penetration following intracerebroventricular administration of Tamiflu • Sleep study in Japanese healthy volunteers

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Appendix 1 Neuropsychiatric Event Categories and Preferred Terms

Category	Preferred Terms
Delirium	Delirium
	Delirium febrile
Delusions/Perceptual disturbance	Delusion
	Delusional perception
	Hallucination
	Hallucination, auditory
	Hallucination, visual
	Hallucinations, mixed
	Illusion
	Paranoia
Panic attack	Panic attack
	Panic reaction
Suicidal events	Completed suicide
	Self injurious behavior
	Self-injurious ideation
	Suicidal ideation
	Suicide attempt
Convulsions	Grand mal convulsion
	Clonic convulsion
	Convulsion
	Epilepsy
	Febrile convulsion
	Partial seizures
	Status epilepticus
	Tonic convulsion
Depressed level of consciousness	Altered state of consciousness
	Consciousness fluctuating
	Depressed level of consciousness
Loss of consciousness	Syncope
	Loss of consciousness

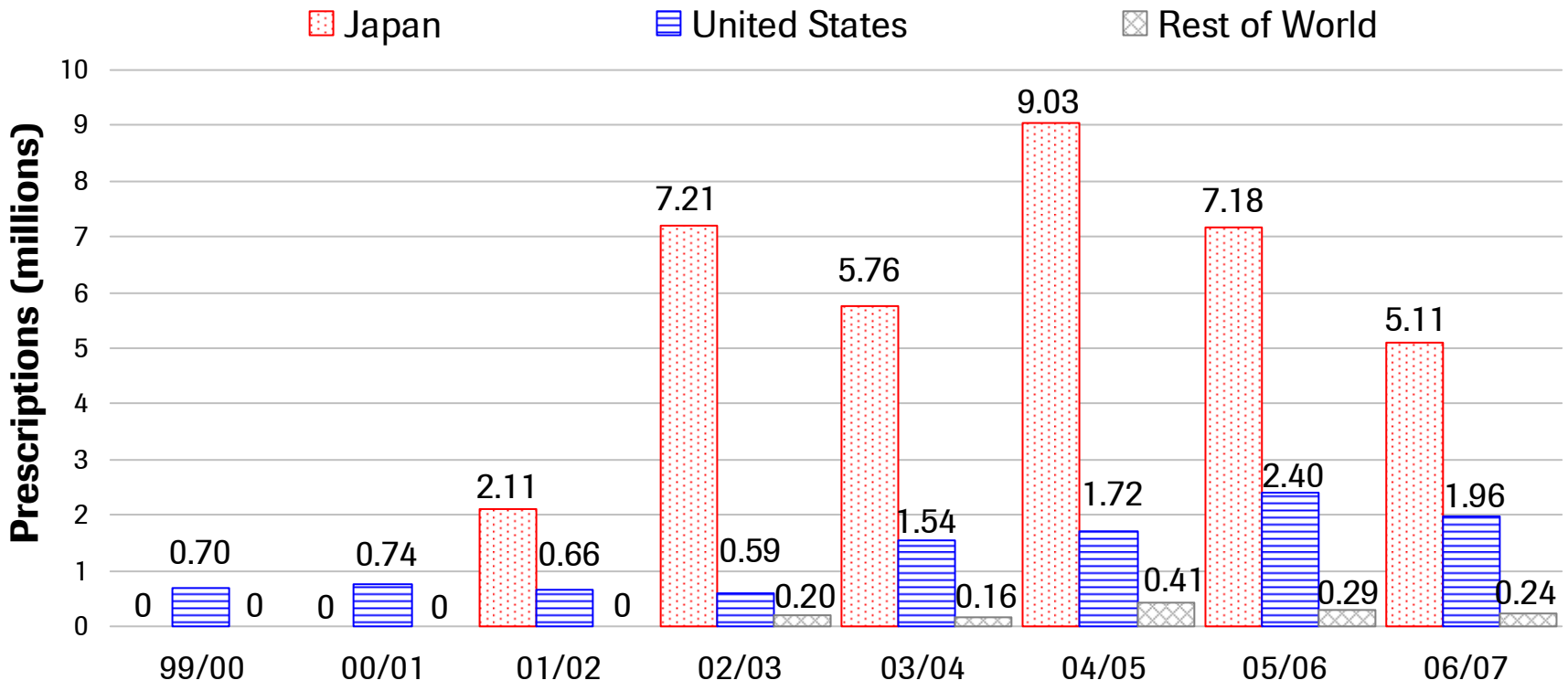
Appendix 1 Neuropsychiatric Event Categories and Preferred Terms (Cont.)

Parasomnia	Abnormal dreams
	Nightmare
	Parasomnia
	Sleep terror
	Sleep walking
	Sleep talking
Accident/Injury	Fracture
	Brain contusion
	Concussion
	Accident
	Accident at home
	Fall
	Injury
	Road traffic accident
	Contusion
	Femur fracture
	Lower limb fracture
	Pelvic fracture
	Fractured coccyx
	Lumbar vertebral fracture
	Rib fracture
	Upper limb fracture
Cognition disturbance	Confusional state
	Disorientation
	Thinking abnormal
	Amnesia
	Global amnesia
	Memory impairment
	Cognitive disorder
	Disturbance in attention
	Mental impairment
	Incoherent
Abnormal behavior	Abnormal behavior
Encephalitis	Encephalitis
	Encephalopathy

Appendix 1 Neuropsychiatric Event Categories and Preferred Terms (Cont.)

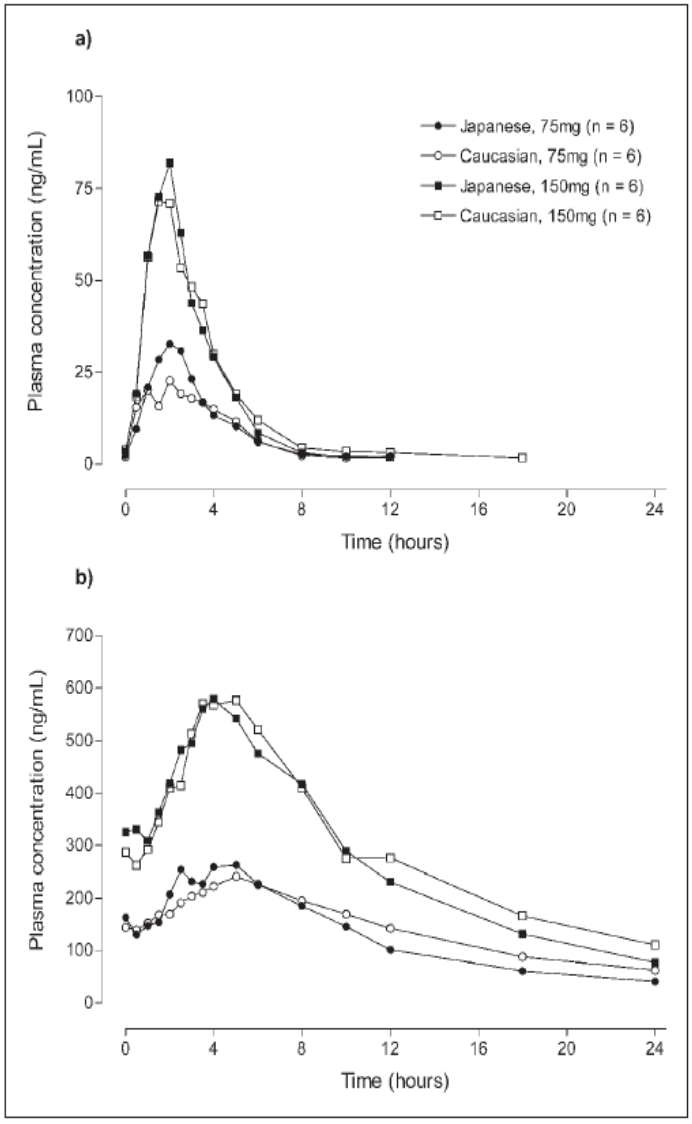
Miscellaneous -- Psych	Anxiety disorder
	Obsessive-compulsive disorder
	Agitation
	Anxiety
	Compulsions
	Nervousness
	Fear
	Restlessness
	Expressive language disorder
	Logorrhoea
	Depressed mood
	Depressive symptom
	Morose
	Affect lability
	Flat affect
	Inappropriate affect
	Anger
	Dysphoria
	Emotional disorder
	Emotional distress
	Euphoric mood
	Moaning
	Mood altered
	Affective disorder
	Apathy
	Listless
	Aggression
	Social avoidant behaviour
	Regressive behaviour
	Hyperventilation
	Choking sensation
	Irritability
	Psychomotor hyperactivity

Appendix 2 Tamiflu Prescriptions by Season and Region: All Ages



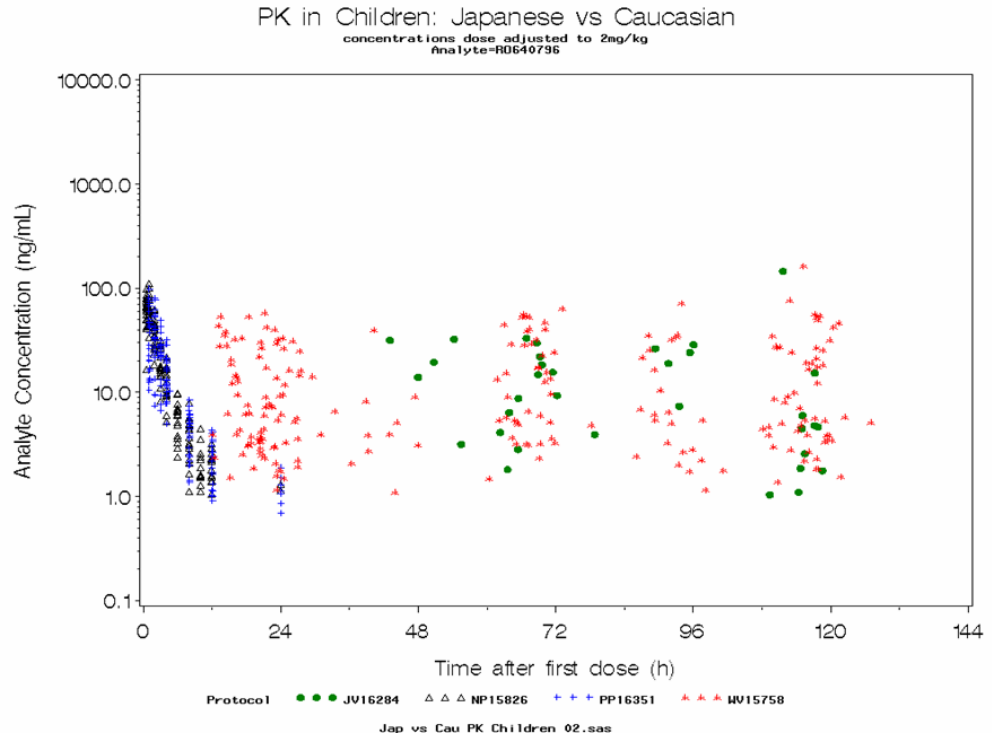
Appendix 3 Exposures of Oseltamivir in Caucasian and Japanese Volunteers Dosed 75 mg and 150 mg bid

a) Oseltamivir b) Oseltamvir carboxylate

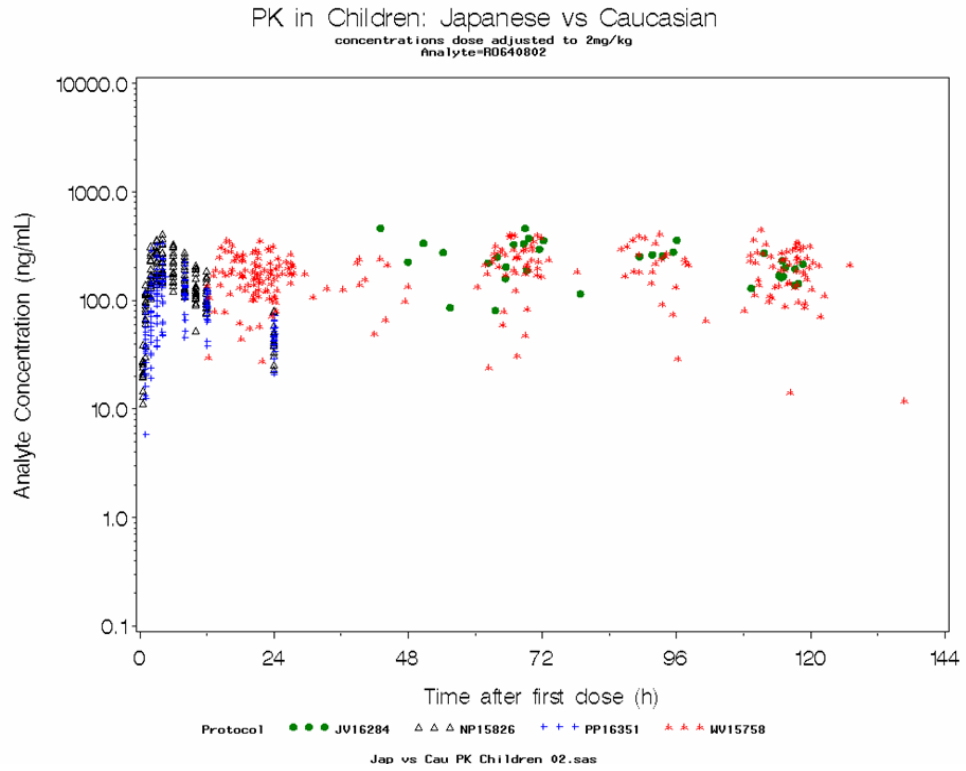


Appendix 4 OP (Panel A) and OC (Panel B) Dose Normalized Exposures in Japanese and and Caucasian Children via Sparse Sampling

Panel A:



Panel B:



Appendix 5 Narratives for MHLW Case Reports

Amantadine

- Four hours after receiving amantadine for treatment of influenza, a < 20 year old male attempted to jump off a balcony when he was stopped by his family. After becoming afebrile, he returned to normal. Amantadine was continued and no further episode of abnormal behavior was reported.

Zanamivir

- On the second day of receiving zanamivir, a < 20 year old female patient suddenly started to shout and tried to go out of a second floor window. Her parents held her down and the event resolved with no recurrence on continuing zanamivir.

No Antiviral Treatment

- A < 20 year old male with fever was observed to have nonsensical thought and speech: "mud is collapsing", "sand is falling from ceiling". He went out of his home to sleep on the road. The next day the patient was diagnosed to have influenza B.

- A < 20 year old male received only an OTC common cold remedy and fell from his apartment on the 9th floor. No one witnessed the fall. At time of death, this person was diagnosed to have influenza A.

- A < 20 year old male, who was diagnosed with influenza with a fever of 39.2°C, was not treated. He became afraid of something and ran to the bathroom, putting his head in the toilet, and saying he wanted to die.

- A < 20 year old female with a temperature of 40°C was diagnosed to have influenza A and did not receive antiviral treatment. She developed disturbed consciousness and hallucination which resolved after a while.

Oseltamivir

- (MCN 479946) A 13 year old boy with a fever of 38.6°C was treated with oseltamivir for an influenza B infection. Some time after taking his second dose, he awoke from sleep and ran out of his house, believing his family was going to harm him. He regained full consciousness one hour later.

- (MCN 483425) A 14 year old female with a fever of 38.2°C was diagnosed with influenza B and took a single dose of oseltamivir. The patient was left home alone and approximately 2.5 hours later was found outside her condominium, lying on the ground, bleeding, apparently having fallen from her apartment. She was brought to the hospital and died one hour later due to traumatic shock. No suicide note was found and an autopsy was not obtained.

Appendix 5 Narratives for MHLW Case Reports (Cont.)

- (MCN483920) A 11 year old male with fever of 39.2°C was diagnosed to have influenza A. Some time after taking a second dose of oseltamivir, he awoke from sleep, hearing a voice saying, "escape". He climbed out the window and ran around his house barefoot, wandered into the rice fields and walked into the river. The episode lasted for approximately 10 minutes and he returned home telling his parents he had gone crazy. Later that evening the patient again heard voices saying, "someone like the Japanese mafia is coming inside" and "escape". His mother calmed him down and discontinued oseltamivir. The following day he was brought to the hospital where his fever, as well as his auditory hallucinations and abnormal behavior, had resolved.

- (MCN487869) A 15 year old male with a fever of 38°C was diagnosed with influenza B. After taking a single dose of oseltamivir, he awoke from sleep and began to walk around his room speaking incoherently. He then suddenly tried to jump from the balcony of his second floor apartment but his mother restrained him. He subsequently went back to sleep and awoke 15 hours later in his normal conscious state; he was afebrile. Oseltamivir was discontinued.