M E M O R A N D U M

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PUBLIC HEALTH SERVICE
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CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: One-Year Post Pediatric Exclusivity Postmarketing Adverse Events Review
Drug: Oseltamivir phosphate
NDAs: 21-087 (Tamiflu® Capsules), 21-246 (Tamiflu® Oral Suspension), Roche
Pediatric Exclusivity Approval Date: March 22, 2004

1. Executive Summary

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of Tamiflu (oseltamivir) in pediatric patients. Up to the "cut off" date of April 22, 2005, AERS contained 1,184 cases for oseltamivir (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent 16% of the total (n = 190).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, March 22, 2004, to March 22, 2005 (referred to hereafter as the *Pediatric exclusivity period*). We used an AERS “cut off” date of April 22, 2005 to allow time for all reports received by March 22, 2005 to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 349 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent 21.8% of the total number of cases (n = 76).

We reviewed 75 unique pediatric cases reported to the FDA during the 13 month period after pediatric exclusivity was granted. Note that raw counts indicate 76 cases; however, one is a duplicate. The 75 cases described eight fatalities (sudden death – 4, cardio-respiratory arrest – 3, and acute pancreatitis with cardiopulmonary arrest – 1), neuropsychiatric events (32), skin/hypersensitivity events (12), gastrointestinal events (6), musculoskeletal events (5), abnormal laboratory tests values events (4), vascular events (2), infectious events (2), hypothermia (2), and one each of a cardiac event and an overdose.

During the first 13 months of pediatric exclusivity period eight deaths were reported. An August 2005 search of AERS identified 4 additional death reports for a total of 12 pediatric deaths all originating from Japan. The reported cause of death in these 12 cases was sudden death (4), cardio-respiratory arrest (4), and one case each of suicide, pneumonia, asphyxiation, and acute pancreatitis with cardiopulmonary arrest (see Appendix 2 for a detailed summary). Since oseltamivir's 1999 approval an increasing number of deaths have been reported to AERS with each influenza season. There is 1 death from the 2000-2001 flu season, 2 from the 2002-2003 season, 5 from the 2003-2004 season and 4 from the 2004-2005 season. These numbers may reflect increased worldwide use of the drug since approval. Deaths from influenza are uncommon among both children with and without high-risk conditions, but do occur. Attribution of causality for the reports of sudden death and cardio-pulmonary arrest are extremely difficult to interpret because there is limited information leading up to the event. These children developed influenza, started therapy with oseltamivir and died suddenly, several of them in their sleep. Nevertheless, any pediatric death is concerning and requests for additional information from both the sponsor and Japanese Ministry of Health have been initiated.

There are 12 cases of skin/hypersensitivity reactions in AERS including Stevens-Johnson syndrome (SJS), anaphylactoid reactions, erythema multiforme, urticaria, toxic epidermal necrolysis, and eczema, associated with the use oseltamivir in treatment of influenza. Toxic epidermal necrolysis, rash, dermatitis, and swelling of the face or tongue are labeled events listed in **ADVERSE REACTIONS** section, under **Observed During clinical Practice for Treatment** subsection. There is one notable case of SJS in a 3-year-old female patient who experienced SJS possibly associated with the use of oseltamivir since the patient did not receive any concomitant medication during three-days of oseltamivir therapy. In addition, there are two cases of erythema multiforme and three cases of anaphylactoid reactions that are possibly related to the use of oseltamivir. Hypersensitivity and serious skin reactions were identified as a potential safety signal that may need to be strengthened in the current oseltamivir product labeling during an earlier review of postmarketing data from the 2004-2005 influenza season. DDRE and the Division of Anti-Viral Products (DAVP) are currently looking into a number of safety issues with oseltamivir and requested the applicant to submit a summary and analysis of these events which we received in June 2005. Submission of additional data from the applicant may be warranted.

The 32 cases of neuropsychiatric related adverse events are also concerning. As with the death reports the majority (31/32) of the cases are from Japan. These cases mostly included reports of delirium, abnormal behavior, hallucinations, convulsions, and encephalitis. Seizures and confusion are the only neuropsychiatric event that is currently labeled for oseltamivir in the US label. A literature search in PubMed did not find any articles of oseltamivir associated with neuropsychiatric events, CNS events, or hallucinations. Nevertheless, the most alarming neuropsychiatric adverse event is the abnormal behavior exhibited by three patients after receiving oseltamivir. A twelve and a thirteen-year-old male

patient jumped out of the second floor window of their homes after receiving two doses of oseltamivir. Head CT scans showed no abnormalities in either patient. A third case was an 8-year-old boy who also exhibited abnormal behavior when he experienced frightening hallucination and rushed out of his house onto the street three hours after receiving his first dose of oseltamivir. He was rescued by his family from potential traffic injury.

With a disproportionate number (69/75 or 92%) of the cases originating from Japan attributing causality to the US pediatric population is difficult. This review raises many unanswered questions with regard to neuropsychiatric events and the deaths. Is oseltamivir dosed differently in Japan compared to the US? Are the neuropsychiatric events an emerging safety signal for oseltamivir that has yet to be reported in the US because of differing prescribing patterns or postmarketing pharmacovigilance? Could these manifestations be due to genetic differences? Do Japanese patients metabolize this drug differently? Is there a role of concomitant use of traditional (herbal) medications to these events? Is there a higher incidence of encephalitis/encephalopathy with Japanese children or an increased susceptibility to influenza-associated CNS events? Addressing these issues is outside the scope of this consult; however the neuropsychiatric events, serious skin/hypersensitivity reactions, and pediatric deaths warrant further investigation and review. We have relayed these questions and concerns to OCTAP and DAVP.

Additional information is needed to assist with the further review of these issues and the following information will be requested from the Sponsor.

1. Detailed summary and analysis of all reported deaths (with autopsy reports if available) in pediatric patients (ages 0 -16 years) for oseltamivir from the date of marketing approval.
2. Detailed summary and analysis of all reports of neuropsychiatric events including reports of delirium, hallucinations, and abnormal behavior in both adult and pediatric patients for oseltamivir from the date of marketing approval.
3. A discussion of the postmarketing safety reporting procedures for Japan and how this compares to US reporting requirements.
4. A discussion of possible reasons for the disproportionate number of reports from Japan.
5. Usage data from Japan compared to US usage data; stratified by age, if possible.
6. An overview of the safety data in the Adverse Reactions section of the Japanese version of the Tamiflu product label and an explanation for difference between the US product insert and the Japanese.

We are also attempting to contact the Pharmaceuticals and Medical Devices Agency (PMDA) that works with the Japanese Ministry of Health, Labor, and Welfare (MHLW) and have recently obtained an English version of the Japanese product labeling for oseltamivir. As discussed with the DAVP, Division of Pediatric Drug Development (DPDD), and the Office of Pediatric Therapeutics during an internal meeting (8-10-05), we will recommend that the following queries be forwarded to the Japanese regulatory authority:

1. We have received twelve reports of deaths in Japanese pediatric patients (ages 0 -16 years) receiving oseltamivir to the FDA's Adverse Event Reporting System (AERS). The Manufacture Control numbers from these 12 reports as identified from AERS are as follows: JP-Roche-254356, JP-Roche-308843, JP-Roche-329358, JP-Roche-359982, JP-Roche-397349, JP-Roche-

397048, JP-Roche-397183, JP-Roche-397182, JP-Roche-397281, JP-Roche-398613, JP-Roche-403186, and JP-Roche-398613. We are particularly interested in these reports because
    a. All of the death reports (n=12) we have received thus far for oseltamivir in pediatric patients are reported from Japan.
    b. Four of these deaths are reported due to "sudden death," an unusual phenomenon in otherwise healthy pediatric patients with influenza.
2. We have received many reports of neuropsychiatric events in Japanese pediatric patients (ages 0 -16 years) that include the following adverse events described as MEDRA preferred terms (PTs): convulsions, encephalopathy, seizures, depressed level of consciousness, loss of consciousness, somnolence, delirium, hallucinations, hallucinations, auditory, hallucinations, visual, nervousness, panic attack, completed suicide, panic attack, restlessness, and abnormal behavior.
    a. Has the Japanese regulatory authority received these reports?
    b. What is the Japanese regulatory authority's interpretation of these neuro-psychiatic adverse event reports?
    c. Were these events considered consistent with the presentation of influenza in the pediatric population in Japan or as possible drug-related events?
3. Could you describe the basis of the regulatory decision to include psychoneurological symptoms, oculomucocutaneous syndrome (Stevens Johnson syndrome) and toxic epidermal necrolysis (Lyell's syndrome) in the PRECAUTIONS/Adverse Reactions section of the Japanese version of the Tamiflu product label?
4. Please provide an overview of the postmarketing safety reporting procedures for Japan and how reports of adverse events are investigated.
    a. General safety reporting procedures and investigative process.
    b. Specifically for oseltamivir, are pharmacovigilance efforts in any way exceptional compared to other marketed prescription products?
    c. Has influenza surveillance and reporting in Japan changed in recent years in light of the risk of avian flu and possible pandemic control measures?
5. Please provide the prescribing patterns and usage data for oseltamivir in Japan. We would appreciate the following specific information if available.
    a. stratification by age
    b. separation by indication (i.e. treatment vs. prophylaxis)
6. We would like to understand medical practices in Japan for influenza management.
    a. What is the approximate use of oseltamivir in otherwise healthy children for both treatment and prophylaxis of influenza?
    b. Are there other treatments for influenza (i.e. nonprescription supplements, herbal remedies, etc.) commonly used in Japan that may have toxicity in children, and/or might interact with oseltamivir if used together?

During the 2004-2005 Influenza season DAVP, ODS, and CDC routinely met to discuss newly submitted postmarketing safety data for all influenza drugs with a focus on special patient populations such as pregnant women and pediatrics with plans to continue this interagency interaction for the 2005-2006 influenza season. We will continue investigate these pediatric adverse events of concern in collaboration with the DAVP and the Division of Pediatric Drug Development and recommend further appropriate action. We will also continue to monitor adverse events in pediatric patients and communicate any other emerging safety signals.

Table of Contents

Section 1: Executive Summary……....1-4

Section 2: Products, Indications, Pediatric Filing History, and Pediatric labeling…...6-7
- 2.1 Products, indications, and dosing…….6
- 2.2 Pediatric filing history……..6
- 2.3 Pediatric labeling……..7

Section 3: AERS Search Results…….7-11
- 3.1 Adverse events in AERS in AERS through April 22, 2005…….7
  - 3.1.1 Counts of reports……7
  - 3.1.2 Reporting trend for pediatric reports through April 22, 2005……8
  - 3.1.3 Top 20 Reported event PTs and labeling status of these events……9
- 3.2 Adverse events from pediatric exclusivity approval date, March 22, 2004 through April 22, 2005……10
  - 3.2.1 Counts of reports……10
  - 3.2.2 Top 20 Reported event PTs and labeling status of these events……10

Section 4: Postmarketing Hands-On Review of All Pediatric Adverse Event Reports from All Sources Received during the Pediatric Exclusivity Period….. 12-22
- 4.1 Demographic characteristics……12
- 4.2 Labeling status of the top 20 reported adverse events and comparison to adult adverse event profile during the pediatric exclusivity period……..12
- 4.3 Fatalities in the pediatric population during the pediatric exclusivity period…..13
- 4.4 Summary of pediatric event profile during the pediatric exclusivity period……15
  - 4.4.1 Neuropsychiatric events……16
  - 4.4.2 Skin/Hypersensitivy events……...18
  - 4.4.3 Gastrointestinal events……..20
  - 4.4.4 Musculoskeletal events……20
  - 4.4.5 Abnormal laboratory test values……21
  - 4.4.6 General events……...21
  - 4.4.7 Vascular events…… 22
  - 4.4.8 Infections…… 22
  - 4.4.9 Overdose event……..22
  - 4.4.10 Cardiac Event……..22

Section 5: Summary…….22-24

Appendix 1……25
Appendix 2……29
Appendix 3……32
Appendix 4……44

2. Products, indications, pediatric filing history, and pediatric labeling

2.1 Products, indications, and dosing in pediatric population

To date there are two approved NDAs with oseltamivir as the active ingredient. Table 1 shows relevant information regarding pediatric use.

Table 1. Oseltamivir approved NDAs up to April 22, 2005

NDA #	Trade name	Dosage form	Approval date	Pediatric indication Pediatric population	Pediatric dose
21-087	Tamiflu® (oseltamivir phosphate) Capsules	Capsule	10-27-99	Treatment of Influenza Treatment of uncomplicated acute illness due to influenza infection in patient 1 year and older who have been symptomatic for no more than 2 days Prophylaxis of Influenza Prophylaxis of influenza in adolescents 13 years and older	>40 Kg or >88 lbs: 75mg twice daily
21-246	Tamiflu® (oseltamivir phosphate) for Oral Suspension	Oral suspension	12-14-00	Treatment of Influenza Treatment of uncomplicated acute illness due to influenza infection in patient 1 year and older who have been symptomatic for no more than 2 days Prophylaxis of Influenza Prophylaxis of influenza in adolescents 13 years and older	≤1 Kg or ≤33 lbs: 30 mg twice daily ≤15 – 23 Kg or ≤33 – 51 lbs: 45 mg twice daily ≤23 – 40 Kg or ≤51 – 88 lbs: 60 mg twice daily >40 Kg or >88 lbs: 75mg twice daily

2.2 Pediatric filing history

Oseltamivir oral capsules were approved on October 27, 1999 for the treatment of uncomplicated acute illness due to influenza infection in patient 1 year and older who has been symptomatic for no more than 2 days. A new indication for prophylaxis of influenza in adults and children 13 years and older was approved on November 20, 2000. The oral suspension was approved on December 14, 2000.

A Pediatric Exclusivity Written Request (WR) was issued on March 1, 2000, and amended on November 25, 2003, The sponsor's response to the WR contained the results of the studies that led to significant updates in pediatric labeling for Tamiflu in all pediatric age groups including pharmacokinetic, dose, safety, and efficacy data in pediatric patients >1 year of age.

Pediatric Exclusivity for Tamiflu was granted on March 22, 2004 on the basis of the submission of these studies.

The labeling supplement incorporating the juvenile animal toxicity data and potential implications for human infants was approved on June 24, 2004: **PRECAUTIONS** section, Pediatric Use subsection, and **ANIMAL TOXICOLOGY** section (see Appendix 1).

2.3 Pediatric labeling

Various sections in the labeling address indication and adverse events in the pediatric population. These are **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION** (see Appendix 1, US version).

A Japanese version of the labeling for **INDICATIONS, DOSAGE AND ADMINISTRATION**, and **PRECAUTIONS** is provided in Appendix 4

3. AERS Search Results

AERS was searched on May 20, 2005, to retrieve reports listing oseltamivir as a suspect drug, in adult and pediatric populations. The search included all sources, foreign and domestic.

3.1 Adverse events in AERS through April 22, 2005

3.1.1 Counts of reports:

Table 2: Raw counts[1] of total oseltamivir reports in AERS through cut-off date of April 22, 2005 (US counts in parentheses)

	All reports (US)	Serious[2] (US)	Death (US)
All ages[3]	1184 (514)	1149(480)	71 (25)
Adults (≥ 17 yrs.)	778 (291)	764 (278)	58 (23)
Pediatrics (0-16 yrs.)	190 (28)	190 (28)	11[4] (0)

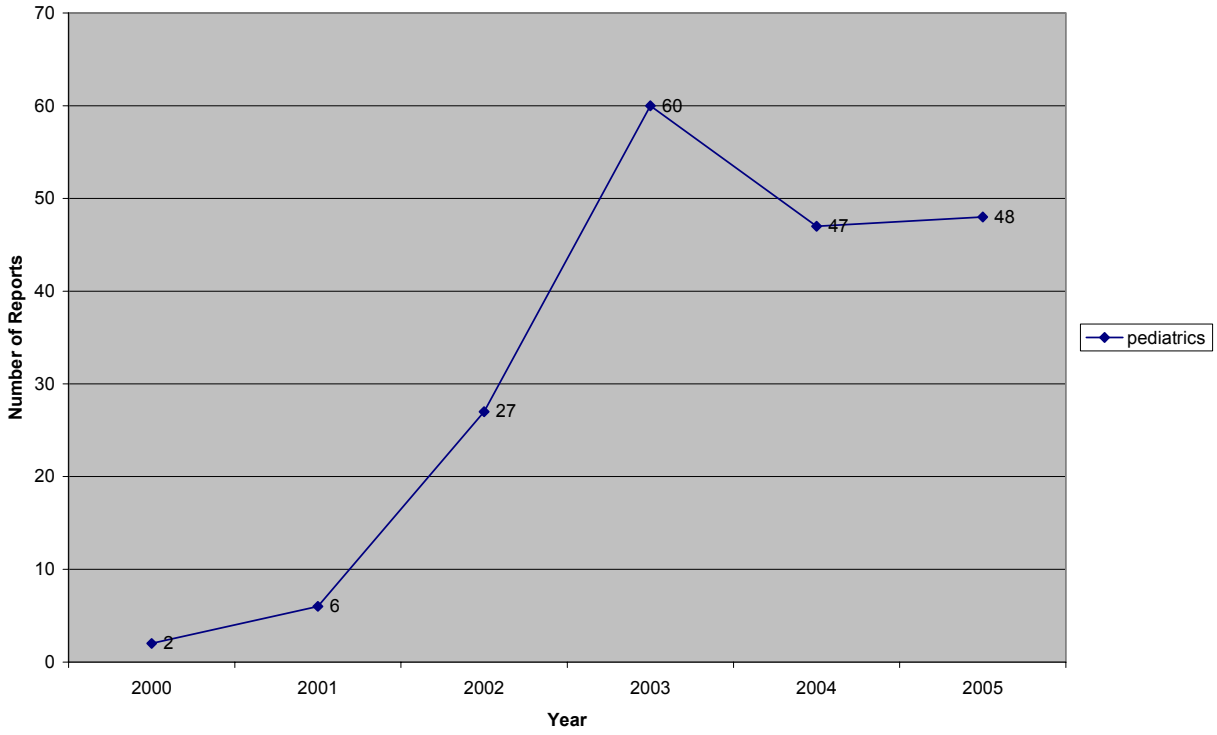
[1] May include duplicates
[2] Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.
[3] Includes reports where age was not provided
[4] One additional death was reported after the April 22, 2005 cut-off date for a total of 12 deaths

3.1.2 Reporting trend for pediatric reports through April 22, 2005:

Table 3: Reporting trend in AERS reports through April 22, 2005[1]		
Number of reports, all ages [2]	**Year**	**Number of pediatric cases (0-16 years)[3]**
247	2000	2
170	2001	6
172	2002	27
180	2003	60
167	2004	47
247	2005	48

[1] Raw counts, may include duplicates
[2] May include reports where age was not specified
[3] Only includes reports where age was listed in the pediatric age grouping of 0-16 years

Figure 1 - Oseltamivir AERS reports in pediatric population up to April 22, 2005



3.1.3 Top 20 reported event PTs and labeling status of these events (underlined denotes unlabeled events):

Table 4: Counts of top 20 reported events (preferred terms) through April 22, 2005[1]		
	Top 20 preferred terms[2]	**Counts**
All ages (including reports where no age was provided)	Vomiting	146
	Nausea	87
	Pyrexia	80
	Diarrhea	63
	Hepatic Function Abnormal	53
	Malaise	52
	Headache	49
	Aspartate Aminotransferase Increased	45
	Alanine Aminotransferase Increased	43
	Cough	39
	Proteinuria	39
	Chromaturia	38
	Dizziness	37
	Dyspnea	36
	Thrombocytopenia	34
	Dehydration	33
	Urine Odour Abnormal	33
	Condition Aggravated	32
	Depressed Level of Consciousness	31
	Insomnia	31
	Platelet Count Decreased	31
	Renal Failure Acute	31
Adults (17+ years)	Vomiting	79
	Pyrexia	68
	Nausea	58
	Hepatic Function Abnormal	46
	Malaise	46
	Alanine Aminotransferase Increased	40
	Aspartate Aminotransferase Increased	40
	Headache	39
	Proteinuria	38
	Chromaturia	36
	Diarrhea	35
	Dyspnea	34
	Cough	33
	Urine Odor Abnormal	33
	Platelet Count Decreased	29
	Thrombocytopenia	28
	Renal Failure Acute	27
	Condition Aggravated	26
	Dehydration	26
	Blood Lactate Dehydrogenase Increased	25
	White Blood Cell Count Increased	25
Pediatrics (0-16 years)	Vomiting	27
	Abnormal Behavior	15
	Delirium	14
	Depressed Level of Consciousness	13
	Diarrhea	12
	Hallucination	11
	Stevens-Johnson Syndrome	11

Table 4: Counts of top 20 reported events (preferred terms) through April 22, 2005[1]		
	Top 20 preferred terms[2]	**Counts**
	Convulsion	10
	Pyrexia	10
	Erythema Multiforme	9
	Loss of Consciousness	9
	Pallor	9
	Nausea	8
	Hepatic Functional Abnormal	7
	Somnolence	7
	Asthenia	6
	Gait Disturbance	6
	Hematemesis	6
	Sudden Death	6
	Tremor	6
[1] Raw counts include terms from duplicate reports [2] Each patient may experience more than one reported adverse event (preferred term)		

3.2 Adverse event from pediatric exclusivity approval date, March 22, 2004 through April 22, 2005:

3.2.1 Counts of reports:

Table 5: Raw counts[1] of total oseltamivir reports from pediatric exclusivity approval date through cut-off date of April 22, 2005 (US counts in parenthesis)			
	All reports (US)	Serious [2] (US)	Death (US)
All ages [3]	349 (37)	342 (30)	23 (3)
Adults (≥17 yrs.)	248 (14)	248 (14)	15 (2)
Pediatrics (0-16 yrs.)	76 (6)	76 (6)	8 (0)
[1] May include duplicates [2] Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other. [3] Includes reports where age was not specified			

3.2.2 Top 20 reported event PTs and labeling status of these events (underlined indicates unlabeled):

Table 6: Counts of top 20 reported events (preferred terms) from pediatric exclusivity through AERS cut off date of April 22, 2005[1]		
	Top 20 preferred terms[2]	**Counts**
All ages (including reports where age is not specified) (total number of adverse events = 349)	Urine Odor Abnormal	33
	Proteinuria	32
	Chromaturia	28
	Vomiting	19
	Malaise	18
	International Normalized Ratio Increased	17
	Convulsion	16
	Diarrhea	16
	Decreased appetite	15
	Hematuria	15
	Depressed Level of consciousness	13
	Hepatic Function Abnormal	13
	Loss of consciousness	13

Table 6: Counts of top 20 reported events (preferred terms) from pediatric exclusivity through AERS cut off date of April 22, 2005[1]		
	Top 20 preferred terms[2]	**Counts**
	Pyrexia	13
	White Blood Cell Count Decreased	13
	Nausea	12
	Blood Creatinine Phosphokinase Increased	11
	Delirium	11
	Platelet Count Decreased	11
	Stevens-Johnson Syndrome	11
Adults (17+ years) (total number of adverse events = 248)	Urine Odor Abnormal	33
	Proteinuria	32
	Chromaturia	28
	International Normalized Ratio Increased	17
	Malaise	17
	Decreased Appetite	15
	Hematuria	15
	Hepatic Function Abnormal	11
	Cardiac Failure Acute	10
	Vomiting	10
	White Blood Cell Count Decreased	10
	Platelet Count Decreased	9
	Blood Creatinine Phosphokinase Increased	8
	Convulsion	8
	Diarrhea	8
	Loss of Consciousness	8
	Nausea	8
	Pyrexia	8
	Rash	8
	Renal Failure Acute	8
Pediatrics (0-16 years)* (total number of adverse events = 76)	Convulsion	8
	Vomiting	8
	Abnormal Behavior	7
	Delirium	7
	Depressed Level of Consciousness	6
	Diarrhea	5
	Hallucination	5
	Loss of Consciousness	5
	Pyrexia	5
	Sudden Death	5
	Crying	4
	Gait Disturbance	4
	Pain in Extremity	4
	Stevens-Johnson Syndrome	4
	Abasia	3
	Blood Creatinine Phosphokinase Increased	3
	Cardio-Respiratory Arrest	3
	Fall	3
	Hematemesis	3
	Somnolence	3

[1] Raw counts include terms from duplicate reports
[2] Each patient may experience more than one reported adverse event (preferred term)

4. Postmarketing Hands-on Review of All Pediatric Adverse Event Reports from All Sources Received During the Pediatric Exclusivity Period (March 22, 2004 to April 22, 2005)

Many of the Japanese cases have reported unusually large daily dosages in grams. In this review, these dosages are denoted in brackets as they are written in the narrative of the cases. Clarification of the actual dose given to the patients has been requested from the applicant as well as the submission of follow-up reports to AERS.

4.1 Demographic characteristics

Our search of the AERS database yielded 75 unique pediatric cases. One of the cases was a duplicate. The demographic characteristics for these 75 cases are listed in Table 7.

Table 7: Characteristics of pediatric cases reported during the 1-year period after receiving pediatric exclusivity (03-22-2004 through 04-22-2005) [n = 75]

Gender [n = 75]	Male:	48
	Female:	27
Age [n = 75]	0-<1 month:	0
(Standard AERS age breakdown)	>1-<2 years:	9
	2-5 years:	25
	6-11 years:	26
	12-16 years:	9
	(mean 7 years, median 6 years)	
Daily dose [n = 35]	Mean:	93 mg
(excluding the overdose case of 300mg dose)	Median:	78 mg
	Range:	25-150 mg
Duration of therapy [n = 72]	Mean:	3 days
(1 dose = 0.5 day)	Median:	3 days
	Range:	0.5 – 9 days
Indications [n = 75]	Influenza	75
Outcomes [n = 75]	Death:	8
	Life-threatening	3
	Hospitalization:	26
	Congenital anomaly:	0
	Disability:	2
	Assessed as medically important:	36
Source [n = 75]	US	5
	Japan	69
	Canada	1

4.2 Labeling status of the top 20 reported adverse events and comparison to adult adverse event profile during the pediatric exclusivity period

For the events listed in this section, any **bolded** event is considered **serious** and any underlined event is considered unlabeled according to the current labeling. Four of the top 20 most frequently reported adverse events in pediatrics during the exclusivity period are serious and labeled: **convulsion**, **vomiting**, **diarrhea**, and **pyrexia**; these events were also reported in the top 20 most frequently reported adverse events in adults.

The other sixteen of the top 20 most frequently reported adverse events in pediatrics during the pediatric exclusivity period are serious and unlabeled: **abnormal behavior**, **delirium**, **depressed level of consciousness**, **hallucination**, **loss of consciousness**, **sudden death**, **crying**, **gait disturbance**, **pain in extremity**, **Stevens-Johnson syndrome**, **abasia**, **blood creatinine phosphokinase increased**, **cardio-respiratory arrest**, **fall**, **hematemesis**, **and somnolence.**

Seven of the 16 reported serious and unlabeled events in pediatrics described neuropsychiatric events: **abnormal behavior**, **delirium**, **depressed level of consciousness**, **hallucination**, **loss of consciousness**, **crying**, and **somnolence**. **Loss of consciousness** is the only unlabeled neuropsychiatric event that had also occurred in the adult population; the pediatric population had 5 reports compared to the 8 reports in the adult population. Although, there are 32 pediatric cases involving the above listed neuropsychiatric events, only one case is reported from the US, the rest are from Japan. It is difficult to make assessments from these foreign reports because many contain concomitant medications that are listed as herbal medications or local medicinal preparations, and many contain administered dosages that appear to be unrealistic. Clarification for these dosages has been requested from the sponsor. It is a concern that mostly healthy young children without any underlying disease took oseltamivir for treatment of influenza and experienced neuropsychiatric events shortly after receiving the drug. The possibility of transient abnormal behaviors due to fever (38 ^{0}C – 39 ^{0}C) could be considered a contributing factor, but this adverse event appeared after the administration of oseltamivir, therefore, the causal relationship of the neuropsychiatric event with oseltamivir could not be excluded. However, further investigation is necessary before recommendations can be made regarding any changes to the current labeling or to conclude that the pediatric adverse event profile was different from that for adult because of the very limited reporting from the US and the concentration of reports coming from one foreign source (i.e. Japan).

The remaining nine unlabeled and serious adverse events in pediatrics described **sudden death**, cardio-respiratory arrest, **gait disturbance**, **abasia**, **fall**, **Stevens-Johnson syndrome**, **pain in extremity**, **blood creatinie phosphokinase increased**, and **hematemesis**. **Blood creatinine phosphokinase increased** is the only unlabeled adverse event from this group among the top 20 reported events that was also reported in the adult population within this period. This abnormal laboratory tests value was associated with **gait disturbance**, **pain in extremity**, and **abasia** that occurred in three patients who concurrently also experienced **rhabdomyolysis**, and **myositis**.

4.3 Fatalities in the pediatric population during the exclusivity period (n = 8)

Table 8: Characteristics of fatal pediatric cases reported during the 1-year period after receiving pediatric exclusivity (03-22-2004 through 04-22-2005) [n = 8]		
Gender [n = 8]	Male: Female:	7 1
Age [n =8]	0-<1 month: >1-<2 years: 2 years: 3 years: 4 years: 9 years: (mean 3.6 years, median 3 years)	0 0 3 2 2 1
Daily dose [n = 1]	39.5mg BID	
Duration of therapy [n = 8]	Mean:	1.6 days

Table 8: Characteristics of fatal pediatric cases reported during the 1-year period after receiving pediatric exclusivity (03-22-2004 through 04-22-2005) [n = 8]		
	Median: Range:	1 day 1-4 days
Indications [n = 8]	Influenza	
Source [n = 8]	Japan	8
Cause [n = 8]	Sudden death Cardio-respiratory Acute pancreatitis	4 3 1

There were eight pediatric reports of death received during the pediatric exclusivity period. One of these reports was incorrectly coded but a correspondence dated June 16, 2005 from the sponsor confirmed that a 4-year-old boy became brain-dead subsequent to therapy with oseltamivir and died in early May. Follow-up information for this case has been requested from the sponsor. All eight reports are from Japan.

Three of the eight patients experienced cardio-respiratory arrest. The 4-year-old male mentioned above **(Case # 5761225**), experienced a distressed feeling of the chest after receiving an unknown dose of oseltamivir. He was hospitalized, and even though the influenza antibody rapid test was negative, his condition deteriorated. He suffered cardio-respiratory arrest and became brain-dead and died two months later. The next patient is a 2-year-old male patient **(Case # 5754754)** with a medical history of hydrocephalus, spinal meningioma excision, meningocele, chiari malformation, ventriculoperitoneal shunt malfunction and epilepsy. He started oseltamivir and the following day he had an oxygen saturation of 86.5% (normal range 94-100%) and a PO_2 of 51.9 mmHg (normal range 90-100 mmHg). Three days later, he experienced cardio-respiratory arrest. His white blood cell count was 24,300 (normal range 4000-9000). The following two days, his urea and electrolyte levels were not within normal ranges, and creatinine kinase was 10 times the upper normal limit. The patient died 2 months later of sepsis. The third patient is a 4-year-old female patient **(Case # 5770409)** who presented at the hospital 3 days after the onset of pyrexia. She was prescribed oseltamivir based on the diagnosis of influenza Type B confirmed by the rapid diagnosis test. She had no history of a preventive vaccination. Physical exam revealed body temperature of 39.3 ^{0}C, mild cough and runny nose, and her general condition was good. That night, after the administration of oseltamivir, vomiting occurred. The next morning, the patient complained of a notable cold feeling and pain in the limbs. About 50 minutes later, she suddenly developed cardio-respiratory arrest, and did not respond to resuscitation.

Four additional cases reported sudden death, and were submitted by the same Japanese reporter from the 2003-2004 influenza season. The reporting physician was concerned about two 2-year old **(Cases # 5758383, 5758385)** and two 3-year old (**Cases # 5757451, 5758389**) male patients who died suddenly while using oseltamivir for the treatment of influenza. None of the patients had received antipyretics, or vaccinations, or had underlying diseases. No abnormal changes were identified prior to the sudden death. Autopsy reports are available for two patients and showed pulmonary edema and brain edema in one and pulmonary edema and a brain herniation in the other.

The remaining case was a report of fatal acute pancreatitis. A 9-year-old male patient **(Case # 4100296)** with history of mental retardation, cerebral palsy, and methylmalonic academia which often included severe acidosis, developed pyrexia of 40 degrees Celsius and tested positive for influenza A. He started oseltamivir therapy 39.5mg twice a day. The patient experienced vomiting over the next two days and

pyrexia persisted. He was hospitalized for fluid replacement and his fever declined. The following morning, the patient developed polypnea, depressed level of consciousness, and acute pancreatitis. Oseltamivir was discontinued. The patient experienced sudden cardio-respiratory arrest in the afternoon; he failed all rescue care and died early next morning of acute pancreatitis. The reporter suspected that the pancreatitis could have been caused by acidosis deterioration and patient's underlying condition.

It is concerning that six young patients died suddenly within one to two days after initiation of oseltamivir therapy. These patients, five males and one female between the ages of two and four years were healthy, had no underlying disease prior to developing influenza. None of the six patients had received a preventative vaccination. In addition, none of the six reports indicated that the patients were considered to be very ill due to the disease. Although these reports do not allow us to assess causality of oseltamivir, the contribution of the drug to the death of these patients, especially with the cases of sudden death and cardio-pulmonary arrest, cannot be excluded based upon the information available.

We performed additional searches in AERS, and found four additional deaths. All four reports originate from Japan. The summary for all 12 deaths is in Appendix 2. One particularly concerning report **(Case # 5787263)** is about a 14-year-old boy who "took his own life" in an hour after he took one capsule of oseltamivir. A 2-year-old boy in second case **(Case # 3894346)** died of cardio-pulmonary arrest the same day he received oseltamivir. The third patient **(Case # 3609833),** a 3-year-old boy who was already in severe medical distress, received oseltamivir for positive influenza test, and subsequently died six weeks later of pneumonia. The last patient **(Case # 3770169),** a 5-year-old female patient who developed asphyxiation characterized with vomiting and sputum one day after receiving oseltamivir, continued oseltamivir therapy for three more days, and died of asphyxiation at an unknown day.

Again, it is difficult to make assessment of the causality of oseltamivir in the death of these young patients due to the limited information provided in the reports. We have planned a join effort between DDRE, DAVDP and OCTAP to communicate with the sponsor to provide a detailed summary and analysis of all reported deaths in pediatric patients from ages 0 to 16 years for oseltamivir from the date of marketing approval.

4.4 Summary of pediatric adverse event profile during the pediatric exclusivity period (excluding fatalities) (n = 67) [Appendix 3]

A hands-on review of the 75 cases in pediatric patients during the pediatric exclusivity period showed that all cases reported a serious outcome by regulatory definition. The 8 fatalities described in section 4.3 are associated with cardio-respiratory arrest (n = 3), sudden death (n= 4) and acute pancreatitis (n = 1), and it will not be discussed in this section. The majority of events reported in the remaining 67 cases was unlabeled or were related to an unlabeled event, and can be generally categorized as neuropsychiatric, skin/hypersensitivity, gastrointestinal (GI), musculoskeletal, abnormal laboratory tests values, general, vascular, infections, overdose, and cardiac events. All 67cases listed influenza as the indication for use.

Each of the ten categories will be discussed separately in the following section. For a detailed summary of the cases in each category, please see Appendix 3.

4.4.1 Neuropsychiatric events (n = 32)

Table 9: Characteristics of neuropsychiatric cases (n = 32)		
Gender (n = 21)	20 M, 12 F	
Age (n = 32)	Mean 8 years , Range 5 months to 15 years	
Daily dose (n = 25)	[8.3 GRAMS BID]*	1
	[3.6 G/2 x2]*	1
	[3.33 GM BID]*	1
	[2 GRAM BID]*	1
	[1.65 GRAMS BID]*	1
	[1.2 GM QD]*	1
	[0.5 G]*	1
	[in a package]*	1
	4mg/Kg/day	1
	150 mg	8
	110 mg	1
	80 mg	2
	78 mg	1
	75 mg	1
	60 mg	1
	40mg	1
	30 – 35 mg	1
Duration of therapy (n = 32)	1 dose	5
	2 doses	12
	2 days	3
	3 days	5
	4 days	4
	5 days	2
	6 days	1
Indication (n = 31)	Influenza	31
Dechallenge (n = 31)	Positive	30
	Negative	1
Outcome (n = 32)	Hospitalization	12
	Life-threatening	2
	Disability	1
	Other	17
Source (n = 32)	US	1
	Japan	31

*Dose clarification has been requested from the sponsor

Thirty-two cases of neuropsychiatric related adverse events were retrieved that included these selective major events: delirium, abnormal behavior, amnesia, restlessness, loss of consciousness, depressed level of consciousness, hallucination, fontanelle bulging, visual disturbance, convulsion, and encephalitis. Only seizure and confusion are labeled events. One of the 32 cases is from the US. Please note that one patient may have experienced adverse events among the six groups listed below; however, each case was included only in the one group that described the major adverse event in that patient.

A. Convulsion (n = 7)

Seven patients experienced convulsions, hallucination, delirium and loss of consciousness after receiving oseltamivir; only seizure is included in the labeling. This group of patients consists of three

male and four female patients with age ranging from ten months to fifteen years. One patient had permanent disability and one with a questionable outcome after having a convulsion and respiratory failure. The confirmation of the outcome for the latter patient has been requested from the sponsor since the report provided no further information except OTHER as the outcome.

B. Abnormal behavior, mental disorder, memory impairment (n = 6)

This group of six reports describes the adverse events of abnormal behavior, mental disorder, and memory impairment. These six male patients are all school-age children from seven to thirteen years who are capable of relating the experiences of their adverse events. The two oldest boys, twelve and thirteen year old, jumped out of the window from a second floor. The older boy remembered the incident but did not know why he jumped from the window. The 12-year-old boy had taken only one dose of oseltamivir 75 mg; he was hospitalized the next day and continued the prescribed 5-day course of oseltamivir therapy. At the time of the event, both patients' body temperature was "between 38 to 39^0C". An 8-year-old boy was rescued by his family from getting hurt when he appeared frightened by something and rushed outside of his house onto the street; this abnormal behavior occurred three hours after receiving one dose of oseltamivir. Oseltamivir therapy was discontinued in five of the six patients after onset of their adverse events. All six patients recovered from their abnormal behavior episode without sequelea.

C. Depressed level of consciousness (n = 6):

Six cases reported depressed level of consciousness, loss of consciousness, delirium, convulsion, aphasia, and dysphonia. There are four male and two female patients with age ranging from five to thirteen years. Oseltamivir therapy was discontinued in four of the six patients after onset of their adverse event; the remaining two patients continued to receive three more days of therapy. It appeared that the duration of the adverse events reported for these six patients is short; patients recovered either on the same day or the next day. A 10-year-old boy incurred a life-threatening injury during his depressed level of consciousness that caused him to fall from the balcony and consequently had to be hospitalized for two months.

D. Visual disturbance, visual hallucination (n = 5)

There are five cases that included adverse events of visual disturbance, visual hallucination, abnormal behavior, and delirium. There are two male and three female patients with age ranging from 19 months to thirteen years. The 13-year-old female patient, who saw things smaller than normal size had dilated pupils and heterotopias/strabismus, she looked at things at an angle. This patient's visual disturbance still persisting four days from the start of the event. Her head CT and blood test revealed no abnormalities.

E. Delirium (n = 4)

There are one female and three male patients with age ranging from three to nine years experienced delirium, fear, and restlessness. During the delirium episode, the 9-year-old boy screamed that he was scared, and the 5-year-old boy ran around the room saying "monster come out." All patients recovered after discontinuation of oseltamivir.

F. Visual disturbance, tremor, excitability, somnolence, fontanelle bulging (n = 4):

This group of four patients consists of two female and two male patients with age ranging from five months to nine years. The adverse events cover miscellaneous unique events including one case of tremor; one case of a child who was overly excited and cried throughout the night; one case of a child who became inactive and somnolent; and one case of an infant with the fontanelle bulging observed by his mother after each administration of oseltamivir throughout the treatment period.

Our review of the 32 cases listing neuropsychiatric adverse events shows that there are unusual and abnormal behavior experienced by a few patients shortly after dosing with oseltamivir (jumping out of a second-story window and frightening hallucinations). However, the quality and information in these reports was limited and a literature search failed to uncover articles associating oseltamivir use with neuropsychiatric event, CNS event, or hallucination. Additional information will be requested.

4.4.2 Skin/Hypersensitivity events (n = 12)

Table 10: Characteristics of skin/hypersensitivity cases (n = 12)		
Gender (n = 12)	4 M, 8 F	
Age (n = 12)	Mean 6 years , Range 2 to 14 years	
Daily dose (n = 8)	80mg	1
	75mg	1
	60mg	1
	56mg	1
	54mg	1
	42mg	1
	40mg	1
	25 mg	1
Duration of therapy (n = 12)	1 dose	3
	2 doses	1
	2 days	1
	3 days	2
	4 days	3
	5 days	2
Indication (n = 12)	Influenza	12
Dechallenge (n = 12)	Positive	12
Outcome (n = 12)	Hospitalization	3
	Life-threatening	1
	Other	8
Source	US	1
	Japan	11
Type of reaction	Stevens-Johnson syndrome	4
	Anaphylactoid reaction	3
	Erythema multiforme	2
	Urticaria	2
	Toxic epidermal necrolysis	1
	Eczema	1

Twelve cases of skin/hypersensitivity reactions were identified in AERS including Stevens-Johnson syndrome SJS), anaphylactoid reaction, erythema multiforme (EM), urticaria, toxic epidermal necrolysis (TEN), and eczema, associated with the use oseltamivir in the treatment of influenza. Note that one case may have more than one adverse event.

Toxic epidermal necrolysis, rash, dermatitis, and swelling of the face or tongue are labeled events listed in **ADVERSE REACTIONS** section, under **Observed During clinical Practice for Treatment** subsection.

One case of SJS (**Case # 5760455**) reported that the adverse event occurred four days after the discontinuation of oseltamivir and phenytoin for convulsion. The patient began to develop exanthema later at night on the same day after receiving azithromycin due to persisting fever. Therefore, oseltamivir would be considered as a co-suspect drug in this case. A second case (**Cases # 5768482**) of SJS also developed four days after discontinuation of oseltamivir; this case listed Flomax and Brufen as concomitant medications that could also be considered co-suspect drugs for SJS. A third case (C**ase # 3961427**) involved SJS and TEN two weeks after oseltamivir therapy had stopped. It is difficult to associate oseltamivir with the cause of SJS and TEN in these three cases.

One notable SJS case in a 3-year-old female patient (**Case # 5769064**) who experienced SJS possibly associated with the use of oseltamivir since the patient did not receive any concomitant medication during the three days of oseltamivir therapy. The rash appeared in the early afternoon, on the same morning the patient first received oseltamivir for influenza. The rash spread to the whole body and erythema appeared around the mouth and the genital area. Three days later, scaling of the external genital and anal areas was noticed. The patient was examined the next day at the dermatology department; scaling and erosive erythema were observed in the mouth, the eyes, the anus, and the external genital area. She was prescribed oral and topical treatment and the scaling around the mouth and eyes subsided a week later.

There are two cases of EM that had many concomitant medications when the adverse event developed. The 5-year-old girl in the first case (**Case # 4125817**) received eight medications a week or less before the start of oseltamivir; thus, it is difficult to associate oseltamivir to be the only suspect drug. Although the 6-year-old boy in the second case (**Case # 5753130**) also received four concomitant medications several months before and at the same time as when oseltamivir was started; however, oseltamivir was the only medication the patient took for the first time when the patient developed generalized erythema.

One notable case of analylactic reaction with swelling of the tongue (**Case # 5726630**) occurred 15 minutes after a 14-year-old male patient had taken his second dose of oseltamivir. The patient was given dephenhydramine and was transported to hospital. His tongue's swelling was significantly worse but he did not experience shortness of breath or rash. His blood pressure was elevated and he was treated with antihistamine, and all symptoms had subsided within two and a half hours. There are two other cases (**Cases # 5780409, 5780410**) of anaphylactoid reaction that did not provide further details to adequately assess the adverse event.

There are two cases of generalized urticaria (**Case # 5758401**) with one case also involved swelling of lips (**Case # 5743106**). The two patients had also received acetaminophen for fever at the same time as oseltamivir therapy. The onset of the adverse events was within one to a couple of hours after oseltamivir administration, and the duration of the events lasted one to three days after treatment with antihistamines and steroids.

In addition to the three notable cases involving SJS, EM and anaphylactic reaction, the two serious

generalized urticaria cases re-confirmed our concern in regard to the serious skin and hypersensitivity adverse events associated with the use of oseltamivir. We have already planned to review all the serious skin and hypersensitivity reports in AERS for all ages, and will communicate our recommendations on strengthening the current approved labeling.

4.4.3 Gastrointestinal events (n = 6)

Table 11: Characteristics of gastrointestinal cases (n = 6)	
Gender (n = 6)	6 M, 1 F
Age (n = 6)	Mean 4 years , Range 1 to 10 years
Daily dose (n = 4)	[1 G BID (=4mg/Kg/day)]* 1 [0.8 G TID]* 1 150mg 1 78 mg 1
Duration of therapy (n = 4)	3 days 1 5 days 2 6 days 1
Indication (n = 6)	Influenza 6
Dechallenge (n = 4)	Positive 4
Outcome (n = 6)	Hospitalization 3 Other 3
Source	US 1 Japan 5

* Dose clarification has been requested from the sponsor

Six cases reported gastrointestinal (GI) adverse events of epistasis, hematemesis, hematochezia, and bowel obstruction during the use of oseltamivir for the treatment of influenza. Epistasis is the only event that is currently labeled. Based on the small number of reports and incomplete information it would be premature to recommend any changes to the current label. DDRE will continue to monitor the above events.

4.4.4 Musculoskeletal events (n = 5)

Table 12: Characteristics of musculoskeletal results cases (n = 5)	
Gender (n = 5)	3 M, 2 F
Age (n = 5)	Mean 7 years , Range 5 to 10 years
Daily dose (n = 2)	70mg 1 2mg/kg BID, then QD 1
Duration of therapy (n = 5)	3 days 1 4 days 1 5 days 3
Indication (n = 5)	Influenza 5
Dechallenge (n = 5)	Positive 3 Negative 2
Outcome (n = 5)	Hospitalization 2 Disability 1 Other 2
Source	US 1 Japan 4

Five patients developed myalgia, myositis, rhabdomyolysis, increased creatitine phosphokinase (CPK), abasia, and severe pain in the muscles associated with the use of oseltamivir for influenza. One case is an US report from Virginia, and the other four cases are from Japan.

Rhabdomyolysis and blood increased CPK have been reported to be associated with influenza viral infection in both pediatric and adult patients[1,2]. Agyeman[3] et al stated that influenza-associated myositis "appears to be more common in childen than in adults, but its age-specific incidence during influenza epidemics is unknown." Christenson[4] et al stated "Of the non-respiratory features of influenza acute myositis is the most prominent and is most likely responsible for the frequent complaint of myalgia in older children and adults. The muscle pain can be severe and incapacitating although transient. Rhabdomyolysis with myoglobinuria develops in occasional patients but is primarily observed in adults. We report a child with influenza A virus infection characterized by severe myalgia, markedly elevated serum myoglobin concentration and myoglobinuria." Although aches and pains are labeled reactions, rhabdomyolysis and blood increased CPK are unlabeled events. There are eight cases of blood increased CPK in the adult population and three cases in children; both counts are among the top 20 adverse events during this pediatric exclusivity period. DDRE will continue to monitor any increased frequency of the following unlabeled adverse events: rhabdomyolysis, increased CPK, and abasia.

4.4.5 Abnormal laboratory tests values (n = 4)

Four Japanese patients reported to have abnormal laboratory tests values involving abnormal liver function, coagulapathy, thrombocytopenia, leukopenia, and neutropenia. Abnormal liver function tests are listed in **ADVERSE REACTIONS** section, under **Observed During Clinical Practice for Treatment** subsection, and under **Digestive**. Coagulapathy, thrombocytopenia, leukopenia, and neutropenia are not included in the current labeling. Since these are all foreign reports from Japan, the information provided limits an in depth analysis of the adverse events. Based on the small number of reports and incomplete information it would be premature to recommend any changes to the current label. We will continue to monitor these events.

4.4.6 General events (n = 2)

Two Japanese patients experienced hypothermia subsequent to treatment with oseltamivir. These patients (4-year old male and 6-year old female) recovered shortly after discontinuation of the drug. The 4-year-old male patient was also concomitantly taking acetaminophen, which may have some contributing factor to the low body temperature. However, according to the report, acetaminophen was stopped a day before oseltamivir was discontinued. Hypothermia is not a labeled event but it would be premature at this time to recommend labeling changes based on two cases. We will continue to monitor this adverse event.

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[1] Leebeek FW, Baggen MG, Mulder LJ, Dingemans-Dumas AM: Rhabdomyolysis associated with influenza A virus infection. *Neth J Med*. 1995 Apr;46(4):189-92.
[2] Singh U, Scheld WM: Infectious etiologies of rhabdomyolysis: three case reports and review. *Clin Infect Dis*. 1996 Apr;22(4):642-9.
[3] Agyeman P, Duppenthaler A, Heininger U, Aebi C: Influenza-associated myositis in children. *Infection* 2004 Aug;32(4):199-203.
[4] Christen JC, San Joaquin VH: Influenza-associated rhabdomyolysis in a child. *Pediatr Infect Dis J.* 1990 Jan;9(1):60-1.

4.4.7 Vascular events (n = 2)

Hypotension occurred in two patients within a few days of dosing with oseltamivir. Both patients were 13-year old Japanese males who recovered after discontinuation of oseltamivir. It is difficult to assess the relationship of hypotension to oseltamivir since both patients were debilitated from the flu, nevertheless, hypotension is not an expected adverse event and we will continue to monitor.

4.4.8 Infections (n = 2)

There are two cases reporting bacterial infections, described as otitis media in one report and as acute bronchitis in the other. Both patients recovered subsequent to antibiotic therapy. Note that these serious reactions may occur as complications of influenza. Otitis media and bronchitisis are labeled events listed in **ADVERSE REACTINS** section, under **Treatment Studies in Pediatric Patients subsection**, in **Table 4**.

4.4.9 Overdose events (n = 1)

Case # 5704370, US: a 2-year-old male patient was given a *single dose* of 25 mL (300 mg) of oseltamivir incorrectly. The prescribed dose was 2.5 mL of oseltamivir oral suspension, which equivalent to 30 mg. The physician reported that "a child was given a 10 times the normal dose and responded positive without any ill effects."

4.4.10 Cardiac events (n = 1)

Case # 5703789, Canada: a 10-year-old male patient began therapy with oseltamivir 40 mg orally twice a day. Three days later he experienced several episodes of asystole, which were observed on the ECG. His heart rhythm returned to normal on the same day without any intervention, and the treatment with oseltamivir was maintained.

5. Summary

The AERS database was searched in May 2005, for reports of adverse events occurring with the use of oseltamivir in pediatric patients. We focused on the one-year period following the approval of pediatric exclusivity (March 22, 2004), although the cut-off date for data collection was extended to April 22, 2005, to allow for all reports received up to the end of March 2005 to be entered in the database.

We found 75 unique unduplicated cases in the 13-month period of review; and in those, unlabeled neuropsychiatric, skin/hypersensitivity, musculoskeletal, abnormal laboratory tests values, and gastrointestinal events were reported in more than one patient. Events reported in only one patient were cardiac arrest and overdose, each event in a different patient. Neither event is included in the labeling of oseltamivir products. During the pediatric exclusivity period, there are only four labeled events: convulsion, vomiting, diarrhea, and pyrexia reported more than once. The majority (92% or 69/75) of the pediatric reports during the pediatric exclusivity period is from Japan, five reports came from US and one came from Canada. All reports listed use for the approved indications.

All 75 cases had a serious outcome, including eight fatalities associated with cardio-respiratory arrest, sudden death, and acute pancreatitis. Three reported life-threatening events: two cases list

neuropsychiatric events (disturbed consciousness in a 10-year old boy who fell from a balcony resulting in injury and "mental disorder" in two 12- and 13-year old boys who jumped out from the second floor of his house) and a third lists Stevens-Johnson syndrome and toxic epidermal necrolysis. Two cases reported disabilities: one described an inability to walk in a 7-year old boy during oseltamivir therapy who recovered after when therapy discontinued; the other involved a 10-month-old boy left with paralysis of right of his body. Twenty-six reported hospitalizations involving twelve neuropsychiatric events, three skin/hypersensitivity events, three gastrointestinal events, three events of abnormal laboratory tests values, two infections events, two musculoskeletal events, and one general event of hypothermia. The remaining 36 cases indicated that the outcome was medically significant, and were captured in the MedWatch form outcome section as "other."

Twelve cases of skin/hypersensitivity reactions were identified in the pediatric exclusivity period including Stevens-Johnson syndrome, anaphylactoid reaction, erythema multiforme, urticaria, toxic epidermal necrolysis, and eczema, associated with the use oseltamivir in treatment of influenza. There is only one notable case in a 3-year-old female patient who experienced SJS possibly associated with the use of oseltamivir since the patient did not receive any concomitant medication during the three days of oseltamivir therapy. In addition, there are cases two cases of erythema multiforme and three cases of anaphylactoid reactions that are possibly related to the use of oseltamivir. Hypersensitivity and serious skin reactions were identified as a potential safety signal that may need to be strengthened in the current oseltamivir product labeling during an earlier review of postmarketing data from the 2004-2005 influenza season. DDRE and the Division of Antiviral Drug Products are currently looking into a number of safety issues with oseltamivir and requested the applicant to submit a summary and analysis of these events which we received in June 2005. Submission of additional data from the applicant may be warranted.

A second group of adverse event that is also concerning are the 32 cases of neuropsychiatric related adverse events. These include delirium, abnormal behavior, amnesia, restlessness, loss of consciousness, depressed level of consciousness, hallucination, fontanelle bulging, visual disturbance, convulsion, and encephalitis. Only one of the 32 cases is from the US. Please note some adverse events may occur among different categorized groups described in section 4.4.1.; patients are grouped by their major adverse events. A literature search in PubMed did not find any article of oseltamivir associated with neuropsychiatric event, CNS event, or hallucination. Nevertheless, the most alarming neuropsychiatric adverse event is the abnormal behaviors exhibited by three patients after receiving oseltamivir. Two twelve and thirteen-year-old male patients jumped out of the second floor window from their home after receiving two doses of oseltamivir. Head CT scan showed no abnormalities in either patient. A third case was an 8-year-old boy who also exhibited abnormal behavior when he experienced frightening hallucination and rushed out of his house onto the street three hours after receiving his first dose of oseltamivir. He was rescued by his family from potential traffic injury.

In summary, in the 13-month period of review the 75 unique pediatric cases showed mostly unlabeled neuropsychiatric, skin/hypersensitivity, musculoskeletal events and abnormal laboratory tests.

With a disproportionate number (69/75 or 92%) of the cases originating from Japan attributing causality to the US pediatric population is difficult. This review raises many unanswered questions with regard to neuropsychiatric events and the deaths. Is oseltamivir dosed differently in Japan compared to the US? Are the neuropsychiatric events an emerging safety signal for oseltamivir that has yet to be reported in

the US because of differing prescribing patterns or postmarketing pharmacovigilance? Could these manifestations be due to genetic differences? Do Japanese patients metabolize this drug differently? Is there a role of concomitant use of traditional (herbal) medications to these events? Is there a higher incidence of encephalitis/encephalopathy with Japanese children or an increased susceptibility to influenza-associated CNS events? Addressing these issues is outside the scope of this consult; however the neuropsychiatric events, serious skin/hypersensitivity reactions, and pediatric deaths warrant further investigation and review. We have relayed these questions and concerns to OCTAP and DAVDP.

Additional information is needed to assist with the further review of these issues and the following information will be requested from the Sponsor.

7. Detailed summary and analysis of all reported deaths (including copies of autopsy reports if available) in pediatric patients (ages 0 -16 years) for oseltamivir from the date of marketing approval.
8. Detailed summary and analysis of all reports of neuropsychiatric events including reports of delirium, hallucinations, and abnormal behavior in both adult and pediatric patients for oseltamivir from the date of marketing approval.
9. A discussion of the postmarketing safety reporting procedures for Japan and how this compares to US reporting requirements.
10. A discussion of possible reasons for the disproportionate number of reports from Japan.
11. Usage data from Japan compared to US usage data; stratified by age, if possible.
12. An overview of the safety data in the Adverse Reactions section of the Japanese version of the Tamiflu product label and an explanation for difference between the US product insert and the Japanese.

We are also attempting to contact the Pharmaceuticals and Medical Devices Agency (PMDA) that works with the Japanese Ministry of Health, Labor, and Welfare (MHLW) and have recently obtained an English version of the Japanese product labeling for oseltamivir. During the 2004-2005 Influenza season DAVDP, ODS, and CDC routinely met to discuss newly submitted postmarketing safety data for all influenza drugs with a focus on special patient populations such as pregnant women and pediatrics with plans to continue this interagency interaction for the 2005-2006 influenza season. We will continue to monitor adverse events in pediatric patients and communicate any emerging safety signals to the Division of Antiviral Drug Products and Division of Pediatric Drug Development.

Appendix 1 (2.3 Pediatric Labeling, US version)

TAMIFLU® (Roche Laboratories)
(oseltamivir phosphate)
CAPSULES
AND FOR ORAL SUSPENSION

CLINICAL PHARMACOLOGY

Pharmacokinetics

Special Populations

Pediatric Patients

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in a single dose pharmacokinetic study in pediatric patients aged 5 to 16 years (n=18) and in a small number of pediatric patients aged 3 to 12 years (n=5) enrolled in a clinical trial. Younger pediatric patients cleared both the prodrug and the active metabolite faster than adult patients resulting in a lower exposure for a given mg/kg dose. For oseltamivir carboxylate, apparent total clearance decreases linearly with increasing age (up to 12 years). The pharmacokinetics of oseltamivir in pediatric patients over 12 years of age are similar to those in adult patients.

INDICATIONS AND USAGE

Treatment of Influenza

TAMIFLU is indicated 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.

Prophylaxis of Influenza

TAMIFLU is indicated for the prophylaxis of influenza in adult patients and adolescents 13 years and older.

TAMIFLU is not a substitute for early vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee.

Description of Clinical Studies: Studies in Naturally Occurring Influenza
Treatment of Influenza

Pediatric Patients

One double-blind placebo-controlled treatment trial was conducted in pediatric patients aged 1 to 12 years (median age 5 years), who had fever (>100°F) plus one respiratory symptom (cough or coryza) when influenza virus was known to be circulating in the community. Of 698 patients enrolled in this trial, 452 (65%) were influenza-infected (50% male; 68% Caucasian). Of the 452 influenza-infected patients, 67% were infected with influenza A and 33% with influenza B.

The primary endpoint in this study was the time to freedom from illness, a composite endpoint which required 4 individual conditions to be met. These were: alleviation of cough, alleviation of coryza, resolution of fever, and parental opinion of a return to normal health and activity. TAMIFLU treatment of 2 mg/kg twice daily, started within 48 hours of onset of symptoms, significantly reduced the total composite time to freedom from illness by 1.5 days compared to placebo. Subgroup analyses of this study by gender showed no differences in the treatment effect of TAMIFLU in males and females.

Prophylaxis of Influenza

The efficacy of TAMIFLU in preventing naturally occurring influenza illness has been demonstrated in three seasonal prophylaxis studies and a postexposure prophylaxis study in households. The primary efficacy parameter for all these studies was the incidence of laboratory confirmed clinical influenza. Laboratory confirmed clinical influenza was defined as oral temperature >/=99.0°F/37.2°C plus at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one

constitutional symptom (aches and pain, fatigue, headache, chills/sweats), all recorded within 24 hours, plus either a positive virus isolation or a fourfold increase in virus antibody titers from baseline.

In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults (aged 13 to 65 years), TAMIFLU 75 mg once daily taken for 42 days during a community outbreak reduced the incidence of laboratory confirmed clinical influenza from 4.8% (25/519) for the placebo group to 1.2% (6/520) for the TAMIFLU group.

In a seasonal prophylaxis study in elderly residents of skilled nursing homes, TAMIFLU 75 mg once daily taken for 42 days reduced the incidence of laboratory confirmed clinical influenza from 4.4% (12/272) for the placebo group to 0.4% (1/276) for the TAMIFLU group. About 80% of this elderly population were vaccinated, 14% of subjects had chronic airway obstructive disorders, and 43% had cardiac disorders.

In a study of postexposure prophylaxis in household contacts (aged >/=13 years) of an index case, TAMIFLU 75 mg once daily administered within 2 days of onset of symptoms in the index case and continued for 7 days reduced the incidence of laboratory confirmed clinical influenza from 12% (24/200) in the placebo group to 1% (2/205) for the TAMIFLU group. Index cases did not receive TAMIFLU in the study.

PRECAUTIONS

Pediatric Use

The safety and efficacy of TAMIFLU in pediatric patients younger than 1 year of age have not been studied. TAMIFLU is not indicated for either treatment or prophylaxis of influenza in pediatric patients younger than 1 year of age because of uncertainties regarding the rate of development of the human blood-brain barrier and the unknown clinical significance of non-clinical animal toxicology data for human infants (see **ANIMAL TOXICOLOGY**).

ANIMAL TOXICOLOGY

In a 2-week study in unweaned rats, administration of a single dose of 1000 mg/kg oseltamivir phosphate to 7-day-old rats resulted in deaths associated with unusually high exposure to the prodrug. However, at 2000 mg/kg, there were no deaths or other significant effects in 14-day-old unweaned rats. Further follow-up investigations of the unexpected deaths of 7-day-old rats at 1000 mg/kg revealed that the concentrations of the prodrug in the brains were approximately 1500-fold those of the brains of adult rats administered the same oral dose of 1000 mg/kg, and those of the active metabolite were approximately 3-fold higher. Plasma levels of the prodrug were 10-fold higher in 7-day-old rats as compared with adult rats. These observations suggest that the levels of oseltamivir in the brains of rats decrease with increasing age and most likely reflect the maturation stage of the blood-brain barrier. No adverse effects occurred at 500 mg/kg/day administered to 7- to 21-day-old rats. At this dosage, the exposure to prodrug was approximately 800-fold the exposure expected in a 1-year-old child.

ADVERSE REACTIONS

Treatment Studies in Pediatric Patients

A total of 1032 pediatric patients aged 1 to 12 years (including 698 otherwise healthy pediatric patients aged 1 to 12 years and 334 asthmatic pediatric patients aged 6 to 12 years) participated in phase III studies of TAMIFLU given for the treatment of influenza. A total of 515 pediatric patients received treatment with TAMIFLU oral suspension.

Adverse events occurring in >1% of pediatric patients receiving TAMIFLU treatment are listed in Table 4. The most frequently reported adverse event was vomiting. Other events reported more frequently by pediatric patients treated with TAMIFLU included abdominal pain, epistaxis, ear disorder, and conjunctivitis. These events generally occurred once and resolved despite continued dosing. They did not cause discontinuation of drug in the vast majority of cases.

The adverse event profile in adolescents is similar to that described for adult patients and pediatric patients aged 1 to 12 years.

Table 4.Adverse Events Occurring On Treatment in >1% of Pediatric Patients Enrolled in Phase III Trials of TAMIFLU Treatment of Naturally Acquired Influenza		
Adverse Event	**Placebo N=517**	**TAMIFLU 2 mg/kg twice daily N=515**
Vomiting	48 (9.3%)	77 (15.0%)
Diarrhea	55 (10.6%)	49 (9.5%)
Otitis media	58 (11.2%)	45 (8.7%)
Abdominal pain	20 (3.9%)	24 (4.7%)
Asthma (including aggravated)	19 (3.7%)	18 (3.5%)
Nausea	22 (4.3%)	17 (3.3%)
Epistaxis	13 (2.5%)	16 (3.1%)
Pneumonia	17 (3.3%)	10 (1.9%)
Ear disorder	6 (1.2%)	9 (1.7%)
Sinusitis	13 (2.5%)	9 (1.7%)
Bronchitis	11 (2.1%)	8 (1.6%)
Conjunctivitis	2 (0.4%)	5 (1.0%)
Dermatitis	10 (1.9%)	5 (1.0%)
Lymphadenopathy	8 (1.5%)	5 (1.0%)
Tympanic membrane disorder	6 (1.2%)	5 (1.0%)

DOSAGE AND ADMINISTRATION

TAMIFLU may be taken with or without food (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**). However, when taken with food, tolerability may be enhanced in some patients.

Standard Dosage - Treatment of Influenza:

Adults and Adolescents

The recommended oral dose of TAMIFLU for treatment of influenza in adults and adolescents 13 years and older is 75 mg twice daily for 5 days. Treatment should begin within 2 days of onset of symptoms of influenza.

Pediatric Patients

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

The recommended oral dose of TAMIFLU oral suspension for pediatric patients 1 year and older or adult patients who cannot swallow a capsule is:

Body Weight in kg	Body Weight in lbs	Recommended Dose for 5 Days	Number of Bottles Needed to Obtain the Recommended Dose
</=15 kg	</=33 lbs	30 mg twice daily	1
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg twice daily	2
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg twice daily	2
>40 kg	>88 lbs	75 mg twice daily	3

An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser. In the event that

the dispenser provided is lost or damaged, another dosing syringe or other device may be used to deliver the following volumes: 2.5 mL (1/2 tsp) for children </=15 kg, 3.8 mL (3/4 tsp) for >15 to 23 kg, 5.0 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

Standard Dosage - Prophylaxis of Influenza:

The safety and efficacy of TAMIFLU for prophylaxis of influenza in pediatric patients younger than 13 years of age have not been established.

The recommended oral dose of TAMIFLU for prophylaxis of influenza in adults and adolescents 13 years and older following close contact with an infected individual is 75 mg once daily for at least 7 days. Therapy should begin within 2 days of exposure. The recommended dose for prophylaxis during a community outbreak of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks. The duration of protection lasts for as long as dosing is continued.

Appendix 2

Appendix 2: Deaths in Pediatric Patients receiving oseltamivir in AERS through August 9, 2005 (N= 12)							
	MFR #	**AERS #**	**Age/Sex**	**Date/Loc.**	**Event**	**Dose/Duration**	**Concomitant Meds**
1	JP-Roche-398613	5761225	4 M	2005 Japan	Cardio-respiratory arrest Anaphylactic shock Brain death Increased myoglobin Increased CPK	Unknown/ 3days	Calonal, Hokunalin, Asverin, Periactin
No influenza Quick test was performed because brother had influenza. Patient experienced a distressed feeling of the chest 3 days after receiving an unknown dose of oseltamivir. An ECG and lab value showed no abnormalities and the patient was discharged. Later that night the patient fell, developed dyspnea and asystole and was admitted to the ER. Patient with increased CPK values and increased myoglobin that continued to increase the next day. He suffered cardio-respiratory arrest and became brain-dead and died 2 months later in May 2005. No autopsy performed.							
2	JP-Roche-397349	5754754	2 M	2005 Japan	Cardio-respiratory arrest Acidosis Brain edema	36mg /3 days	phenobarbital
A male patient with a medical history of hydrocephalus, spinal meningioma excision, meningocele, chiari malformation, ventriculoperitoneal shunt malfunction and epilepsy. He started oseltamivir and the following day he had an oxygen saturation of 86.5% (normal range 94-100%) and a PO_2 of 51.9 mmHg (normal range 90-100 mmHg). Three days later, he experienced cardio-respiratory arrest. His white blood cell count was 24,300 (normal range 4000-9000). The following two days, his urea and electrolyte levels were not within normal ranges, and creatinine kinase was 10 times the upper normal limit. The patient died of sepsis over 2 months after receiving oseltamivir.							
3	JP-Roche-399699	5770409	4 F	2005 Japan	Cardio-respiratory arrest Sudden death	Unknown/1 day	Calonal, periactin, mucosal
4-year-old female patient who presented at the hospital 3 days after the onset of pyrexia. She was prescribed oseltamivir based on the diagnosis of influenza Type B confirmed by the rapid diagnosis test. She had no history of a preventive vaccination. Physical exam revealed body temperature of 39.3 ^{0}C, mild cough and runny nose, and her general condition was good. That night, after the administration of oseltamivir, vomiting occurred. The next morning, the patient complained of a notable cold feeling and pain in the limbs. About 50 minutes later, she suddenly developed cardio-respiratory arrest, and did not respond to resuscitation.							
4*	JP-Roche-397183	5758383	2 M	2002-2003 Japan	Sudden death Pulmonary edema Brain edema	Unknown/1-2 days	Unknown
Newspaper report concerning children that died suddenly during sleep. Patient had not received a vaccination or an antipyretic and had no underlying diseases. One to days after starting therapy with oseltamivir for the treatment on influenza A during the 2003-2004 flu season the patient died suddenly in his sleep at midnight. No abnormal changes were noticed before the death. An autopsy was performed and pathology findings reported brain edema and pulmonary edema.							
5*	JP-Roche-	5758385	2 M	2002-2003	Sudden death	Unknown/1-2 days	Unknown

Appendix 2: Deaths in Pediatric Patients receiving oseltamivir in AERS through August 9, 2005 (N= 12)							
	397182			Japan			
Newspaper report concerning children that died suddenly during sleep. Patient had not received a vaccination and it is unknown if received an antipyretic. He had medical history of asthma. One to days after starting therapy with oseltamivir for the treatment on influenza A during the 2003-2004 flu season the patient died suddenly in his sleep at midnight. No abnormal changes were noticed before the death. An autopsy was performed but the child's guardians would not allow the release of the pathology findings.							
6*	JP-Roche-397048	5757451	3 M	2002-2003 Japan	Sudden death	Unknown/1-2 days	Unknown
Newspaper report concerning children that died suddenly during sleep. Patient had not received a vaccination or an antipyretic. And had no underlying diseases. One to days after starting therapy with oseltamivir for the treatment on influenza A during the 2003-2004 flu season the patient died suddenly in his sleep during an afternoon nap. No abnormal changes were noticed before the death. An autopsy was performed but the child's guardians would not allow the release of the pathology findings.							
7*	JP-Roche-397281	5758389	3 M	2002-2003 Japan	Sudden death Brian herniation Pulmonary edema	Unknown/1-2days	Unknown
Newspaper report concerning children that died suddenly during sleep. Patient had not received a vaccination or an antipyretic. He had a history of asthma One to 2 days after starting therapy with oseltamivir for the treatment on influenza A during the 2003-2004 flu season the patient died suddenly in his sleep during an afternoon nap. No abnormal changes were noticed before the death. An autopsy was performed and pathology findings reported cerebellar tonsillar herniation and pulmonary edema.							
8	JP-Roche-359982	4100296	9 M	2004 Japan	Acute pancreatitis	79mg/4 days	Glucose, Meylon, Gaster, Epogin, Mucodyne, Flagyl, LAC B-R, Oryzatym, sodium bicarbonate,
A 9-year-old male patient with history of mental retardation, cerebral palsy, and methylmalonic academia which often included severe acidosis that inproved with blood transfusions, developed pyrexia of 40 degrees Celsius and tested positive for influenza A. He started oseltamivir therapy 39.5mg twice a day. The patient experienced vomiting over the next two days and pyrexia persisted. He was hospitalized for fluid replacement and his fever declined. The following morning, the patient developed polypnea, depressed level of consciousness, and acute pancreatitis. Oseltamivir was discontinued. The patient experienced sudden cardio-respiratory arrest in the afternoon; he failed all rescue care and died early next morning of acute pancreatitis. Reporter suspected that the pancreatitis could have been caused by acidosis deterioration and the patient's underlying condition.							
9	JP-Roche-403186	5787263	14 M	2005 Japan	Completed Suicide	Unknown/1 day	***Unknown***
Patient took one capsule and then he took his own life within an hour**.**							
10	329358	3894346	2 M	2002 Japan	Sudden Death cardio-pulmonary arrest Myocarditis	50mg/1 day	Periactin, Asverin, Bisolvon,
Diagnosed with varicella in early Dec 02. Three weeks later diagnosed with flu and oseltamivir was started. Also with mild pseudocroup was							

Appendix 2: Deaths in Pediatric Patients receiving oseltamivir in AERS through August 9, 2005 (N= 12)							
observed but no retractive breathing so patient not hospitalized. However the patient's respiratory status deteriorated later that day and he was hospitalized and an airway was secured. On route to another hospital the patient went into cardio-pulmonary arrest and resuscitation was attempted but the patient died. No convulsions were observed. Myocarditis and encephalitis due to influenza were suspected. No autopsy was performed.							
11	254356	3609833	3 M	2000 Japan	Pneumonia Encephalopathy Convulsions Cerebral edema Renal failure Subarachnoid hemorrhage	25mg/5 days	Diclofenac cefditoren
Patient developed a fever and was administered a diclofenac suppository and the fever resolved. He was then taken to the hospital and administered cefditoren. The patient then starting talking nonsense and developed convulsions that lasted 10 minutes. He had a fever of 42C. He was treated with diazepam and phenytoin but went into a coma. The patient continued to deteriorate and was admitted to the ICU and diagnosed with a brain herniation. An influenza test was positive so oseltamivir and amantadine were started. Oseltamivir was discontinued 5 days later. CTscan revealed brain edema and subarachnoid hemorrhage. The patient died 6 weeks later of pneumonia**.**							
12	308843	3770169	5 F	2002 Japan	Vomiting asphyxiation	150mg/4 days	Cefdinir, Ketotifen, cromoglicic acid
Patient started oseltamivir and cefdinir. The next day developed asphyxiation characterized with vomiting and sputum. Cefdinir was stopped. 3 days later oseltamivir was stopped. At an unknown date the patient died of asphyxiation.							

* All from the same reporter (a physician): Newspaper report concerning children that died suddenly during sleep.

Appendix 3
Summary of pediatric adverse event profile during the pediatric exclusivity period excluding fatalities (n = 67)

1. Neuropsychiatric events (n = 32)

A. Convulsion (n = 7)

Case # 4164460, Japan: a 15-year-old female patient started oseltamivir 150mg QD for flu. Two days later she had a convulsion. She went to the hospital where a diagnosis of epilepsy was made. Oseltamivir was discontinued. The patient was given anticonvulsants and the epilepsy improved.

Case # 5769078, Japan: a 15-year-old male patient treated with oseltamivir 75mg BID for influenza. One hour later, the patient started saying nonsensical words while walking around with a stoned-like expression. His right upper extremities became bent and rigid, his body leant to the left, and he could not stand by himself without support from the family. He needed help to be put on a stretcher because his body was ankylosed. The patient then collapsed and lost consciousness. He was hospitalized, oseltamivir treatment was stopped. A head CT scan and a brain wave examination showed no abnormality. His temperature was 38.1^0C upon arrival to the hospital and came down to 37.6^0C after admission with stable vital signs. The patient felt unsafe and could not sleep, so the monitor was removed t midnight. At 0300h, the patient suddenly stood up and left the bed, he pulled an intravenous line; he was called down and put back to sleep by his family. The patient did not remember this incidence. The patient's condition improved over the next two days and was discharged from the hospital. Two weeks after his discharge from the hospital, an electroencephalographic examination was performed and showed spine-like spikes brainwaves in several parts of the top of the head. The physician commented that it is difficult to determine whether the EEG abnormality had been present from the beginning or it occurred after the episode of the convulsion and the delirium. The patient has no documented past history of convulsion or spasmodic disorder.

Case # 5704342, US: a 13-year-old female patient with history of asthma received treatment with oseltamivir 75 mg QD for an unknown indication. The patient experienced a fever and seizure with 25 minutes of confusion. She was admitted to the emergency room and treatment with oseltamivir was stopped. The seizure and fever resolved ten days later. An EKG and CT scan were normal, a lumbar puncture was negative, and the urinalysis was unremarkable, blood work was performed.

Case # 4172810, Japan: a 13-year-old male patient started oseltamivir 75 mg in the morning for flu. The patient took the second dose later that afternoon, suddenly; he became unconscious and had a convulsive seizure. It was stated that oseltamivir was brought up. The patient was hospitalized and the same day he also experienced hallucinations. Treatment with oseltamivir and all concomitant drugs were stopped. Six days later, the convulsion, hallucination and loss of consciousness resolved.

Case # 5758386, Japan: a 6-year-old female patient diagnosed with influenza started oseltamivir [3.33 GM twice a day]* in the morning. No observation of the condition of the patient after the first dose was available because her family was out all day while she was at home. When the mother returned at 1700h, the patient was shivering. The patient's mother thought the shivering would improve if she was given another dose of oseltamivir. But in fact, this made the shivering worse. One hour after the second

dose, the patient experienced convulsions throughout the body. She had difficulty speaking with slurring of words; she appeared to be in a state of hallucination and kept on shouting the word "photograph." The following day oseltamivir was discontinued and the patient was taken to the hospital as her fever persisted. The patient was admitted and given fluids for dehydration. No convulsion had occurred, her fever resolved by the evening, and her hallucinations resolved four days later.

Case # 5767192, Japan: a 5-year-old female received oseltamivir for influenza. Two or three hours later she experienced convulsion and respiratory failure, no further information was provided on whether the patient lived or died. This report listed OTHER as outcome. The actual outcome for this case has been requested from the sponsor.

Case # 5681976, Japan: a 10-month old male patient began therapy with 30 to 35 mg of oseltamivir once a day for treatment of influenza. The following day, the patient developed encephalitis and had a convulsion. Oseltamivir therapy continued three more days before stopping. At the time of reporting, which was nine months after the event day, the infant was left with paralysis of the right side of his body.

B. Abnormal behavior (n = 6)

Case # 5769789, Japan: a 13-year-old male patient tested positive for influenza started oseltamivir 75 mg twice a day in the afternoon for his first dose. He took his second dose seven hours later at night as instructed. About 2.5 hours later, he jumped from the second floor of his house. His lower body was deep in the snow that had accumulated outside of the house. He got out of the snow by himself, rang the doorbell, and entered the house. He repeatedly said "I am no half asleep," and went back to his room and slept. At that time his body temperature was 38^0C. He did remember the incident but did not know why he jumped from the window. He was examined at the hospital by a physician who commented liver function abnormality from the lab data seemed to be due to hepar adiposum (fatty liver). Brain MRI, EEG, and brain CT were performed with no abnormality observed. Blood samples showed no abnormality either.

Case # 4176012, Japan: a 12-year-old male patient diagnosed with influenza B received oseltamivir 75 mg twice a day and cefditoren pivoxil. His body temperature was 38-39^0C. On the same day about 2100h, the patient complained of suffering from an abnormal look (different from usual) and jumped down from he upstairs window at home. He was transported to the hospital the next day around noon awake and alert. His pulse rate = 100, blood pressure = 120/70 mmHg. The abnormal behavior reported to have resolved on the same day. He was hospitalized for five days. Head CT scan and electroencephalography showed no abnormalities. Oseltamivir was discontinued the same day the patient was discharged.

Case # 4104815, Japan: a 12-year-old male patient received oseltamivir 75 mg twice daily for suspicion of flu. He was also taken a cold preparation concomitantly. The next day, the patient's temperature was 39^0C and he began to behave abnormally suddenly. He became normal again after taking a shower. He also had urine incontinence. Later that day, patient behaved abnormally again saying" I'm visiting grandparent's on the mother's side" and attempting to walk in completely different directions from the exit. He was admitted to the hospital for observation and oseltamivir was discontinued. His abnormal behavior resolved the next day. CT scan of the head and an electroencephalogram were normal. Blood

test indicated that his monocyte percentage and lactate dehydrogenase level were high. Four days later, the patient was discharged from the hospital.

Case # 4141886, Japan: An 8-year-old male patient started oseltamivir 80 mg daily for suspicion of flu. A couple of hours after receiving oseltamivir, the patient woke up from his sleep and moaned but could no speak. He pointed to the garbage can and threw the TV remote control and pants away. He also carried the bedclothes to the toilet, brought plates from the kitchen and wrote a letter on the plates. The patient was hospitalized for his abnormal behavior. While in the hospital, the abnormal behavior did not reoccur. The patient was discharged three days later.

Case # 5768481, Japan: an 8-year-old male patient with positive test for influenza received oseltamivir 55 mg around 1030h and went to bed. He woke up around 1330h, immediately, he had hallucination and showed abnormal behavior. He seemed frightened by something and rushed outside to the street. The patient's mother was worried about not being able to stop her son rushing to the street if other family would not happened to be around to help her. The mother took oseltamivir one month before and experienced hallucination of the cars from the opposite direction was all heading toward her. The patient was examined at the clinic again, he received normal saline intravenously and the symptoms subsided.

Case # 4088682, Japan: a 7-year-old male patient started oseltamivir 80mg QD for flu. Two days later, his mother found him restless and talking illogically. The patient experienced memory impairment and a behavior disorder. Oseltamivir was discontinued. The following day while at school, the patient experienced significant abnormal character (letter) recognition. He was taken to a hospital and the restlessness was confirmed. An X-ray showed gas in the patient's small intestine and "GE" was performed for massive gas. The behavior disorder and restlessness continued to the next week. The patient showed slight improvement for the correctness in responding to questions. He remembered the places he put things that he had previously forgotten. One month later, the patient's dysgraphia was reported as improved. The physician stated that the patient had a tendency to experience constipation and the patient's consciousness became clear and returned to normal sense after a bowel movement.

C. Depressed level of consciousness (n = 6):

Case # 5761228, Japan: a 13-year-old female patient started oseltamivir 25mg twice a day for treatment of influenza. Three days later, half an hour after taking a late supper, The patient suddenly fell and lost consciousness for about ten seconds with ill complexion that lasted for about ten minutes. She presented at the hospital, alert and regained consciousness. Her electrocardiogram and blood test were normal. Electroencephalogram performed a week later did not show abnormality. Whole brain MRI performed the following week was also normal.

Case # 4167021, Japan: a-12-year-old male patient diagnosed with flu and began treatment with oseltamivir 60 mg daily and intravenous (IV) fluids for prophylaxis of dehydration. While at home, his temperature was noted to be 41.7^0C and he developed consciousness clouding, shrill, moan, delirious utterances, incontinence of speech and hyperanakinesia in a high pitched voice, had round eyes and was talkative for 40 minutes. Two hours later, the patient recovered. The patient visited the clinic again and was treated with IV fluids as prophylaxis for dehydration and treatment with oseltamivir was continued for another two days.

Case # 5739308, Japan: a 12-year-old male patient diagnosed with influenza and started oseltamivir. He took oseltamivir twice and lost consciousness twice in the morning for about ten minutes each episode. He was hospitalized for suspected influenza encephalopathy. His level of consciousness was clear and no abnormality was observed in his data including the blood sample and CT.

Case # 4163919, Japan: a-10-year-old male patient diagnosed with flu received oseltamivir 75 mg twice a day. Three to four hours after his first dose, the patient developed life-threatening consciousness disturbance and fell down from a balcony injuring his spleen, nasolacrimal duct, pneumothorax of the right lung and breaking the wrists and right ileum requiring hospitalization for two months. The patient reported to "walking around under automatic behavior" while in a fever for the past few days. The outcome of the disturbed consciousness is unknown.

Case # 5769052, Japan: an 8-year-old female patient diagnosed with influenza and treated with oseltamivir. The following day she experienced disturbed consciousness. She was admitted to the hospital and oseltamivir was discontinued. The patient responded properly to the instruction: "please stand up, raise your right hand, and stand on your left leg." However, she was unable to respond to the question about her name, age and "who is he?" as the physician pointing to her father. The next morning twelve hours later, she was able to answer correctly to all the questions from the night before, and she did not remember anything about being examined at the emergency room and her admission to the hospital.

Case # 5760451, Japan: a 5-year-old male patient tested positive for flu and was given oseltamivir [1.2 GM once daily]*. Ten seconds later the patient experienced disturbed consciousness and vomiting. He recovered quickly the same day and he was examined at the hospital. He regained consciousness, no paralysis was observed. Oseltamivir was discontinued and the vomiting resolved that day. The patient's body temperature was recorded twice as 39.4 and 39.2 degrees Celsius. Head CT scan showed no abnormality. Three days later the fever had subsided and the following day the patient was discharged. The patient reported to have recovered from the influenza four days later.

D. Visual disturbance, visual hallucination (n = 5):

Case # 4079852, Japan: a 13-year-old female patient treated with oseltamivir 75 mg BID for flu. Three days after the initiation of oseltamivir therapy, the patient reported to see things smaller than normal size, and she looked at things at an angle. The patient had dilated pupils and heterotopias/strabismus. Treatment with oseltamivir and concomitant drugs were stopped. The symptoms did not improve three days later and the patient was examined by an ophthalmologist who did not find any abnormality in the patient's eyes. Head CT and blood test revealed no abnormalities. The visual disturbance was persisting four days from the start of the event.

Case # 5745851, Japan: a 9-year-old female patient received oseltamivir for influenza. The patient vomited, started to cry and complained of hallucination of things were looking bigger. Oseltamivir was discontinued.

Case #5762519, Japan: a 6-year-old male patient tested positive for influenza received oseltamivir 2mg/Kg twice a day. The next night, patient suddenly woke up and began to laugh loudly and say "I

can't take this off" and "OK" repeatedly, moving hands as if he was pinching something. He was having a fever of more than 39 degrees Celsius. The following morning, the patient showed the same actions as the night before; he had fever more than 43 degrees Celsius. It was observed that the patient also said "I can't catch the bug" and he went back to sleep. The patient did not remember the incident. The patient visited the hospital the next morning; the consciousness was confirmed to be normal. However, the patient developed fever again at night and the hallucination continued for the next two day until his fever resolved with a temperature of 36.8 degrees Celsius.

Case # 5745849, Japan: a 5-year-old female patient was prescribed oseltamivir without performing a diagnostic test because her grand mother had influenza. She took oseltamivir [two grams twice daily]*. The next morning her fever subsided. On the fifth day of therapy, she woke up earlier than usual feeling dizzy with everything turning around, she started crying, saying "mom's face looks bigger for a second and then smaller the next." The abnormalities continued for four hours until her mother decided to take her to the hospital. She was having difficulty in walking straight for a few meters to the bicycle from the entrance of the house. While riding the bicycle together, her mother found nothing unusual in patient's speech. The visual disturbance and light-headed feeling disappeared by the time they arrived to the hospital. The patient was hospitalized and examined by the departments of ophthalmology and of otology, no particular problem was found. Oseltamivir was stopped. MRI was performed and showed no abnormality. Similar symptoms had not occurred during her hospitalization. The physician was concerned about the events because they occurred after fever had subsided.

Case # 5745862, Japan: a 10 month-old male patient started oseltamivir therapy for flu. Two days later he was hospitalized after experiencing morose and visual hallucinations. The patient was found groping with his hand in the air as if he could see something. He cried and grizzled. The influenza virus was not detected in a flu antibody rapid test. An EEG was negative for influenza encephalopathy or encephalitis. Oseltamivir was discontinued and the patient was hospitalized for observation. Five days later the morose and visual hallucination resolved and the patient was discharged from the hospital.

E. Delirium (n = 4)

Case # 5761188, Japan: This literature case cited a 9-year-old male patient started oseltamivir for influenza once per day. In the evening he came down the stairs screaming "I'm scared, help!" He looked weak in his knees and the collapsed. He was taken to the hospital and was administered intravenous fluids. He was admitted to the hospital for delirium and oseltamivir was discontinued. The patient was treated with dexamethasone and glycerol. He continued in his state of delirium, restlessness, or suddenly got up and clung to his mother looking scared. He answered the questions about his name and age slowly after a pause, but gave no answer about his grade after thinking about it for a while, and then he lied down on the bed. He developed amnesia. The delirium resolved a week later.
Noboru Igarashi et al. *Japanese Journal of Pediatrics*. 58:183, 2005. A case of a Boy with Persistent and Relapsed Alteration of Consciousness, Anxiety and Amnesic Symptoms in the Phase of Cure and Recovery from Type-A Influenza.

Case # 5759346, Japan: a 7-year-old male patient received oseltamivir [1.65 GRAM twice a day] for flu. One day later he experienced delirium in saying nonsensical words and oseltamivir therapy was discontinued. The following day the patient recovered.

Case # 4167023, Japan: a 5-year-old male patient with a temperature of 38.9^{0}C received 78 mg oseltamivir daily for flu. Over night, his fever increased to 40^{0}C and he developed delirium tearing around the room saying "monster come out." The following morning his temperature came down to 37.6^{0}C and the delirium resolved the same day. The patient continued to be afebrile through the next day, oseltamivir was discontinued the following morning and the event did not reoccur.

Case # 5772597, Japan: a 3-year-old female patient received one dose of oseltamivir for treatment of flu. She experienced delirium, the patient's parents decided to discontinue oseltamivir. At the time of the report, delirium resolved.

F. Tremor, excitability, somnolence, fontanelle bulging (n = 4)

Case # 4154498, Japan: a 9-year-old female patient received oseltamivir [3.6G/2 x 2]*for flu. The patient experienced tremor thirty minutes after oseltamivir administration in the evening. The next day in the evening tremor occurred again after oseltamivir administration. The pharmacist advised the patient's mother to discontinue oseltamivir therapy. The patient visited the clinic the next morning, oseltamivir was discontinued. The patient was reported by her mother as being in a stable condition. The outcome for the tremor is reported as unknown.
Case # 5770414, Japan: a 1-year-old female patient with a fever of 38.9 degrees Celsius that continued for four days, she was tested positive for flu and was prescribed oseltamivir. Although the fever subsided by the next night, the dose of oseltamivir had been decreased, the patient was "overly excited and cried her lungs out during the night." Oseltamivir was discontinued. Diazepam 4mg suppository was prescribed. In the morning, the patient's steps were unsteady. At night due to the excitement, diazepam suppository was prescribed again. Neither nausea nor vomiting occurred. "There was no Uchal rigidity and Kernig's sign." Two days later, the excitement began to subside. Her walking returned to normal. Three days after discontinuation of oseltamivir, the excitement subsided, and the patient started walking and playing with toys.

Case # 5762496, Japan: a 1-year-old male patient diagnosed with influenza started oseltamivir 20 mg twice a day. Oseltamivir discontinued two days later. The patient's fever resolved on the fourth day and the patient became inactive and tended to be somnolent without convulsion. The patient was given IV fluids for suspicion of dehydration at the hospital four days from the stop of oseltamivir therapy. He was admitted the next day to the hospital due to his fever reoccurred with a body temperature of 38.7^{0}C, blood pressure of 114/52 mmHg and pulse rate of 154 beats/minute. The patient remained inactive and somnolent. On day after hospitalization, the patient had a CT scan which was normal, body temperature was 37.2^{0}C, pulse rate was 142 beats/minutes and he started to regain his appetite. Two days later, the patient was discharged from the hospital and recovered to his normal activity and appetite.

Case # 5759348, Japan: a 5-month-old male infant was given oseltamivir due to the whole family had contracted flu. Half and hour after receiving oseltamivir, the patient vomited a lot when his mother noticed the patient's large fontanelle bulging developed. The patient was examined the next day at the hospital and the results of physical examination were normal as the fontanelle was flattened (2 cm) and oseltamivir therapy continued. The patient received his evening dose of oseltamivir, he did not vomit, but again he developed the bulging of the fontanelle, which the mother described as like "a ping-pong ball." The reporting of the phenomenon of the bulging of the fontanelle was only observed by the patient's mother who described "the large fontanelle bulged at one or two hours after administration of

oseltamivir in the evening and returned to the usual size by the morning of the following day, which was repeatedly observed during the period the patient was taking the drug." This adverse event was observed throughout the treatment period of eight days. The physician denied of having actually seen the bulging of the fontanelle.

2. Skin/Hypersensitivity events (n = 12)

Cases # 5780409, Japan: a 5-year-old female patient with history of asthmatic attack started oseltamivir [1 GRAM twice a day] to treat influenza. On the same day, she experienced anaphylactoid reaction. Four days later oseltamivir was discontinued, the event of anaphylactoid reaction improved on the same day.

Case # 5780410, Japan: a 3-year-old female patient started oseltamivir [0.55 GRAMS twice daily]* for influenza. Two days later, she experienced anaphylactoid reaction. A further two days later oseltamivir was discontinued and the patient reported to be recovering the following day.

Case # 5758401, Japan: a 2-year-old female patient diagnosed with influenza received oseltamivir 25 mg once daily. One hour late, she developed redness and welts on her upper limbs and thighs bilaterally. The next hour, the redness and welts expanded down her left lower limbs, and continued to both the lower limbs. She presented to the hospital three hours later and was diagnosed with urticaria. She was treated with diphenhydramine and cortisone, but the urticaria had spread to the whole body and her fever increase to over 40 degrees Centigrade. The patient subsequently recovered after the following day. Base o the results of drug-induced lymphocyte stimulation test (DLST), the physician considered that the generalzed urticaria was caused by oseltamivir.

Case # 5758401, Japan: a 9-year-old female patient received oseltamivir for flu. She developed swelling of the lips and urticaria a couple of hours later. The patient was treated with betamethasone and chlorpheniramine maleate for three days, the swelling of lips resolved.

Case # 5726630, US: a 14-year-old male patient with a fever of 101.7^0 F received oseltamivir and ibuprofen for influenza. The patient experienced projectile vomiting on the same he received one dose of oseltamivir. He was able to keep down his lunch the next day, and his fever decreased to 101.4^0 F. He received another dose of oseltamivir that evening, 15 minutes later he experienced "an anaphylaxis reaction with swelling of the tongue." The patient was given two Benadryl tablets and was transported to the hospital. The patient's blood pressure was elevated, his tongue swelling was significantly worse, but no shortness of breath or rash was observed. He was treated with antihistamine and all of his symptoms subsided within 2.5 hours.

Swelling of the tongue is a labeled reaction.

Case # 5769064, Japan: a 3-year-old female patient was diagnosed with influenza and was prescribed oseltamivir for three days. Despite the popular rash appeared after the initiation of oseltamivir, the patient completed the therapy. The rash spread to the whole body and erythema appeared around the mouth and genital area. The day after completion of oseltamivir therapy, scaling of the external genital and anal areas was noticed on the patient. The patient was examined the following day at the dermatology department; scaling and erosive erythema were observed in the mouth, the eyes, the anus,

and the external genital area. She was given oral and topical treatments for her conditions and her symptoms subsided one week later. The patient did not receive any concomitant drug, and oseltamivir was considered to be the cause of the SJS event.

Case # 5760455, Japan: a 6-year-old female patient was hospitalized for pyrexia associated with flu; she received 5-day therapy of oseltamivir, and phenytoin for convulsion. Four days after completion of oseltamivir therapy, azithromycin was started due to persisting fever. That night, she developed exanthema on her extremities and over her face, and bulbar conjunctiva hyperemia also developed three days later. She was treated with steroids and recovered one week later. It is difficult to establish the relationship of SJS with oseltamivir because there are two other co-suspect drugs also involved. Oseltamivir was already stopped for four days when the adverse event started.

Case # 5768482, Japan: a 10-year-old male patient started a 5-day therapy of oseltamivir 75 mg for flu. On the fourth day the patient suffered from Stevens-Johnson syndrome which required hospitalization. Oseltamivir discontinued on the same day. The patient had no fever, his appetite was poor, stomatitis occurred, and wheal appeared mainly on his extremities. The patient recovered subsequently one month later.

Case # 3961427, Japan: an 11-year-old male patient started oseltamivir and cefteram for the treatment of flu accompanied with fever. Both drugs were stopped after two days. One week later, patient complained of pharyngeal pain and photophobia. Cefteram was restarted the next day. The patient then was diagnosed with measles, then mumps, and the manifestations of SJS and TEN. It is difficult to associate oseltamivir with SJS and TEN since these adverse events started two weeks after 2-day therapy of oseltamivir. Other concomitant cephem and macrolide antibiotics were on going while the manifestations of SJS and TEN started.

Case # 5743106, Japan: a 6-year-old male patient started treatment with oseltamivir for flu. He developed generalized erythema multiforme three days later and oseltamivir was discontinued. He was hospitalized, erythema multiforme continued to manifest over the next two days, he was treated with topical steroid and the event resolved.

Case # 4125817, Japan: a 5-year-old female patient experienced erythema multiforme during the use of oseltamivir for flu. Erythema multiforme started developing after three days of oseltamivir therapy. She was treated with topical steroid and oral antihistamine. The event of erythema multiforme resolved six days after the discontinuation of oseltamivir.

Case # 4113526, Japan: a 3-year-old female patient with asthma developed one papule after received one dose of oseltamivir as her mother had contracted influenza. The patient subsequently was hospitalized three days later with influenza and was treated with oseltamivir 28 mg twice a day. The following day, she developed eczema. She was treated with oxatomide, and antihistamine and released form he hospital. The next day, patient developed eruption that extended from the face to the trunk and extremities. Oseltamivir was discontinued. Her symptoms and eczema resolved over the next two days.

3. Gastrointestinal events (n = 6)

Case # 5765051, Japan: a 1-year-old male patient received oseltamivir for influenza. The next day, he experienced hematemesis once and was hospitalized for dehydration. Oseltamivir was discontinued, and

patient was transferred to anther hospital and received fluids. The patient's fever was still persisting four days later and he was given zanamivir.

Case # 5779779, Japan: a 9-year-old female patient was diagnosed with influenza and was given oseltamivir 75 mg. One hour later, bleeding spot appeared on her face, she felt queasy without abdominal pain and experienced hematemesis twice. The patient was treated with Solu-Cortef 250mg and recovered after two hours.

Case # 5739306, Japan: a 1-year-old male patient received oseltamivir 20mg BID for 4 days to treat influenza and Cefcapene Pivoxil HCL for possible pneumonia. He experienced nose bleed two days later and vomited large amount of blood. The patient was hospitalized the following day, oseltamivir was discontinued, and Zanamivir started. The reporting physician was unclear whether the vomited blood was from the nose bleed or actually from gastrointestinal hemorrhage.

Case # 5754726, US: a 10-year-old male patient took one dose of oseltamivir 60mg suspension orally and immediately vomited so violently that he vomited blood. This report was considered medically significant due to the event of vomiting blood.

Case # 5767187, Japan: a 1-year-old male patient who was hospitalized for hematochezia that occurred only once during his oseltamivir therapy for treatment of influenza; he had since recovered.

Case # 4120795, Japan: This case reported bowel obstruction two days after initiation of oseltamivir for treatment of flu. A 2-year-old male patient was hospitalized with a diagnosed ileus, but the X-ray revealed a great deal of gas; he was given an enema, then developed diarrhea and was placed on a fasting and fluid infusion. He was discharged from the hospital four days later with improvement.

4. Musculoskeletal events (n = 5)

Case # 4093849, Japan: a 5-year-old female patient received oseltamivir (35 mg PO BID for 5 days) for flu. The next day she had back and abdominal pain and developed increased CPK. Oseltamivir was decreased to 27 mg PO BID. Two days later, she developed myalgia of the lower extremities especially in the calf muscle and was unable to walk. On the fifth day of therapy, oseltamivir was discontinued due to worsening of the symptoms. Laboratory tests revealed elevated WBC, neutrophils, monocytes, AST, ALT, CPK, and S-myoglobin. The lymphocytes were low; blood and protein were detected in the urine. The patient's abnormal laboratory test values continued to be elevated until she was discharged from the hospital 12 days later. It was reported that the patient's renal function may have been decreased due to her urinary tract infection.

Case # 5777920, US: a 7-year-old male patient experienced pain in his leg on the first day receiving oseltamivir for influenza. He was limping on the second day, and on the third, he was unable to walk- abasia and had to crawl and had to ask for help to move around. The patient vomited a dose of oseltamivir and the drug was discontinued. The patient's adverse events improved.

Case #5743086, Japan: this 7-year-old male patient experienced muscle pains on both legs three days after receiving oseltamivir. He reported that the pain was so strong that he could barely walk- abasia. Laboratory tests revealed increased CPK. The status of the patient's recovery was not provided.

Case # 4151173, Japan: an 8-year-old male patient developed myositis during the use of oseltamivir for flu. The patient developed lower femoral pain without fever three days after start of oseltamivir; he was also unable to take an upright position due to pain. He was hospitalized on the fifth day at the completion of oseltamivir therapy due to his inability to walk- abasia with a fever of 37.6 degrees Celsius. Laboratory tests revealed remarkably increased CPK. The patient's pain improved the next and the myositis resolved three days later.

Case # 5756044, Japan: a 10-year-old female patient experienced gait disturbance on the fourth day of oseltamivir therapy. She hospitalized, she only received one dose of oseltamivir on her fifth day of therapy. Her gait disturbance improved and she was discharged from the hospital five days later with resolution. Laboratory data showed C-reactive protein, alkaline phosphatatase, and lactate dehydrogenase levels to be above expected normal high ranges.

5. Abnormal laboratory tests values events (n = 4)

Case # 4084401, Japan: a 3-year-old male patient with history of refractory epilepsy with complex convulsions was receiving valproic acid, phenytoin and clonazepam. The patient received oseltamivir [1 G twice daily (= 4 mg per Kg per day)]* and cefpirome for suspicion of flu and hyperthermia. Two days after the initiation of oseltamivir, blood test revealed abnormal liver transaminases and abnormal coagulation, urinalysis revealed abnormal renal function. Oseltamivir and cefpirome were discontinued. A liver protection drug, VK3 and antithrombin 3 preparations were administered. The patient improved the following day. Two weeks later, the patient's liver function tests were normal. One week later renal function returned to normal. Test for a variety of viruses all proved negative. The reporter stated that the patient took oseltamivir in 2001 – 2002 season, and hepatic or renal function disorder was not observed.

This is a literature case: Ito N: Pronounced Hepatic and Renal Dysfunction during Oseltamivir Administration in a Boy Taking Multiple Anticonvulsants for Epilepsy…Japanese Society of Emergency Pediatrics 2004; 3(1):98.

Case # 4113537, Japan: a 4-year-old male patient with history of epilepsy and mental retardation was receiving valproic acid. Three days after oseltamivir [0. G TID]* for treatment of influenza, the patient experienced thrombocytopenia. "Laboratory tests showed that his platelets were decreased at 49,000. Two days later, he was found to have a platelet count of 15,000, and he underwent further examination at a university, where his platelet were found to be 10,000, and he was admitted to hospital and oseltamivir was discontinued. Over the following two days, his platelets started to increase, and four days after discontinuing oseltamivir laboratory tests showed his platelets had increased to 230,000."

Case # 4138589, Japan: a 5-year-old male patient tested positive for influenza received oseltamivir 39 mg twice a day. The patient developed gastrointestinal symptoms with coughing and vomiting one hour after the first dose of oseltamivir. During the night, he had hyperthermia and was in a "twilight state with delirious utterances" but had no subsequent vomiting. The following day, he had diarrhea, coughing became aggravated with no lowering of his fever. Two days later the patient was hospitalized for bronchitis, decreased WBC (leucopenia) and thrombocytopenia. Oseltamivir had been discontinued the previous evening as the patient had been on therapy for five days. He was treated with clindamycin IV. Five day later Leukopenia and thrombocytopenia resolve and the patient was discharged from the hospital fifteen later.

Case # 5728347, Japan: an 11-year-old female patient tested positive for influenza and treated with oseltamivir 75mg twice a day. The patient had also a medical history of diarrhea due to infectious enteritis until a week ago before having the flu. The next day, the patient experienced terrible dizziness, vomiting and diarrhea. The patient continued to take oseltamivir with no improvement. Five days later, she experienced neutropenia, and decreased WBC. The patient was treated with cetocef, metoclopromide and IV fluids. The patient recovered from the diarrhea and vomiting the next day and recovered from neutropenia and decreased WBC six days later.

6. General events (n = 2)

Case # 5740041, Japan: a 4-year old male patient experienced hypothermia that ranged between 34 to 36 degrees Celsius after receiving oseltamivir. After discontinuation of the oseltamivir therapy, the body temperature rose to 36 degrees Celsius two days later.

Case # 5767194, Japan: a 6-year-old female patient experienced hypothermia that ranged between 34 to 36 degrees Celsius after receiving oseltamivir. On the same day that oseltamivir therapy was stopped, the body temperature rose to 36 degrees Celsius.

7. Vascular events (n = 2)

Case # 4083694, Japan: A 13-year old male patient received oseltamivir 75 mg twice a day for treatment of diagnosed flu. On the same day, he developed abdominal pain and diarrhea. He then blacked out, fell and developed incontinence. He was hospitalized; hypotension (BP: 73/33 mmHg, P: 72/min) and abdominal tenderness were observed. The patient was treated with oxygen and IV fluids. He recovered the next day (BP: 92/54 mmHg, P: 76/min) after discontinuation of oseltamivir.

Case # 4121669, Japan: A 13-year old male patient was treated with oseltamivir for four days; he experienced aphose and orthostatic hypotension three days later. The recorded blood pressure one day after the incidence was 102/54 mmHg. The patient recovered completely from his episode of orthostatic hypotension one month later.

8. Infections (n = 2)

Case # 4147667, Japan: a 1-year old female patient started oseltamivir 20 mg twice a day for flu. A day later, she was hospitalized for otitis media, diarrhea and dehydration. The patient was treated with piperacillin and fluids; she was discharged three days later with resolution of otitis media, pain and anxiety. Oseltamivir was discontinued. Diarrhea and dehydration also resolved at a later time.

Case # 4127588, Japan: a 12-year old male patient with a history of bronchial asthma and stridor was treated with oseltamivir 150mg daily for the onset of flu and fever. The patient was hospitalized two days later for acute bronchitis; he was treated with clarithromycin 200mg twice a day for five days with no improvement. Cefzodin sodium was then given intravenously three times a day; the patient's acute bronchitis resolved on the same day.

9. Overdose events (n = 1)

Case # 5704370, US: a 2-year-old male patient was given a *single dose* of 25 mL (300 mg) of olseltamivir incorrectly. The prescribed dose was 2.5 mL of oseltamivir oral suspension, which equivalent to 30 mg. The physician reported that "a child was given a 10 times the normal dose and responded positive without any ill effects." *The sponsor has been contacted to provide further clarification regarding dose administration.*

10. Cardiac events (n = 1)

Case # 5703789, Canada: a 10-year-old male patient began therapy with oseltamivir 40 mg orally twice a day. Three days later he experienced several episodes of asystole, which were observed on the ECG. His heart rhythm returned to normal on the same day without any intervention, and the treatment with oseltamivir was maintained.

Appendix 4 (Pediatric Labeling, Japanese version)

Revised: July 2005 (12th version of new form)

Standard Commodity Classification No. of Japan
87625

- INFLUENZA ANTIVIRAL AGENT -

TAMIFLU® Capsule 75

<Oseltamivir phosphate formulation>

Designated drug and Prescription drug [Note 1)]

WARNING
(1) The necessity of TAMIFLU for treatment or prophylaxis should be carefully examined before use. [See <Precautions regarding Indications>]
(2) Prophylaxis of influenza viral infections is based on vaccine therapy. Note that the prophylactic use of TAMIFLU is not an alternative to vaccine therapy.

CONTRAINDICATIONS (TAMIFLU is contraindicated in the following patients.)
Persons with known hypersensitivity to any of the components of TAMIFLU

INDICATIONS
Treatment or prophylaxis of viral infection of influenza A and B

<Precautions regarding Indications>
1. Considering that the anti-viral agent is not necessarily essential for all patients with influenza A and B viral infections, the need for treatment with TAMIFLU should be carefully examined by thoroughly observing the condition of patient.
2. For the prophylaxis of influenza, TAMIFLU should be principally administered to family members or persons living with patients with influenza viral infections. Also, these people should meet the following criteria:
   (1) Elderly (65 years or more)
   (2) Patients with chronic respiratory or cardiac diseases
   (3) Patients with metabolic disorders such as diabetes mellitus
   (4) Patients with renal dysfunction (See <Precautions regarding Dosage and Administration>)
3. The safety and efficacy of TAMIFLU in infants under 1 year old (low birth weight infants, newborns, and nursing infants) have not been established (See “Pediatric Use”).
4. TAMIFLU is not effective against infections other than influenza A and B viral infections.
5. TAMIFLU is not effective against bacterial infections (See “Important Precautions”).

DOSAGE AND ADMINISTRATION

1. Treatment of influenza
   The usual oral dosage for adults and children weighing 37.5 kg or more is 75 mg as oseltamivir twice a day for 5 days.
2. Prophylaxis of influenza
   The usual oral dosage for adults and children aged 13 years or more is 75 mg as oseltamivir once a day for 7 to 10 days.

	Treatment	Prophylaxis
Targets of administration	Adults and children weighing 37.5 kg	Adults and children aged 13 years or more
Regimen	Oral 75 mg twice daily	Oral 75 mg once daily
Duration of	5 days	7 to 10 days

therapy		

<Precautions regarding Dosage and Administration>

1. In treatment with TAMIFLU, TAMIFLU administration should be started within 2 days after the onset of influenza-like symptoms (data supporting the efficacy of TAMIFLU have not been obtained from subjects who started treatment after 48 hours from the onset of symptoms).
2. In prophylaxis of influenza with TAMIFLU, attention should be paid to the following:
   (1) TAMIFLU administration should be started within 2 days after contact with patients with influenza viral infections (data supporting the efficacy of TAMIFLU have not been obtained from persons who started drug administration after 48 hours from contact with patients with influenza viral infections).
   (2) The prophylactic effect of TAMIFLU against influenza viral infections can be maintained by repeated administration.
3. Since the plasma concentration increases in the adult patients with impaired renal function, the following regimen is recommended corresponding to a decrease in renal function (according to the overseas results). TAMIFLU has not been used in children, etc. with impaired renal function.

Creatinine clearance (mL/min)	Regimen	
	Treatment	Prophylaxis
Ccr>30	75 mg twice daily	75 mg once daily
10<Ccr≤30	75 mg once daily	75mg on alternate days
Ccr≤10	The recommended dose has not been established.	

Ccr: Creatinine clearance

PRECAUTIONS

1. Careful Administration (TAMIFLU should be administered with care in the following patients.)
   Patients with severe impaired renal function (See <Precautions regarding Dosage and Administration> and “Important Precautions”).

2. Important Precautions
   (1) Since TAMIFLU is a renal excretion type drug, the plasma concentration may be increased in patients with decreased renal function. Accordingly, cautious administration is required based on <Precautions regarding Dosage and Administration> corresponding to the creatinine clearance value in the use while observing the clinical condition (See [PHARMACOKINETICS]).
   (2) Since bacterial infection may be complicated with <Reference> influenza viral infection or misjudged as influenza-like symptoms, appropriate measures should be taken such as administration of anti-bacterial agents if bacterial infection is suspected (See <Precautions regarding Indications>)

3. **Adverse Reactions**

Adverse drug reactions were observed in 85 cases (27.5%) among the 309 cases investigated up to the approval of TAMIFLU Capsule. Most frequently reported adverse drug reactions were abdominal pain (21 events, 6.8%), diarrhea (17 events, 5.5%), nausea (12 events, 3.9%), etc. (at the time of approval). Adverse drug reactions occurred in 35 cases (50.0%) among the 70 cases investigated up to the approval of Dry Syrup (infants and children aged 1-12 years old). Most frequently reported adverse drug reactions were vomiting (17 events, 24.3%), diarrhea (14 events, 20.0%), etc. (at the time of approval).

(1) Clinically significant adverse reactions

1) Shock, anaphylactoid reactions (frequency unknown): Shock and anaphylactoid reactions may occur, and the patient should be observed carefully and if symptoms such as urticaria, facial and laryngeal edema, dyspnea, blood pressure

decreased appear, the administration should be discontinued and appropriate measures should be taken.

2) Pneumonia (frequency unknown):
Pneumonia has been reported to occur. If any abnormality is observed, causes (e.g. drug-induced, infectious) should be determined by examinations such as radiography, and appropriate measures should be taken.

3) Hepatitis, hepatic function disorder, jaundice (frequency unknown): Hepatitis, hepatic function disorder, and jaundice accompanied by marked increase of AST (GOT), ALT (GPT), γ-GTP, and Al-P may occur. The patient should be carefully monitored and if any abnormality occurs, the administration should be discontinued and appropriate measures should be taken.

4) Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome) (frequency unknown): Skin disorders such as oculomucocutaneous syndrome (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell's syndrome) may occur. The patient should be monitored carefully and if these symptoms occur, the administration should be discontinued and appropriate measures should be taken.

5) Acute renal failure (frequency unknown): Acute renal failure may occur. Patients should be carefully monitored and if any abnormality is observed, the administration should be discontinued immediately and appropriate therapeutic measures should be taken.

6) Leucopenia, thrombocytopenia (frequency unknown): Leucopenia and thrombocytopenia may occur. Patients should be carefully monitored and if any abnormality is observed, appropriate measures, such as discontinuing treatment, should be taken.

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

8) Hemorrhagic colitis (frequency unknown): Hemorrhagic colitis may occur. If any abnormality is observed such as bloody stool, bloody diarrhea, etc., the administration should be discontinued and appropriate measures should be taken.

(2) Other adverse reactions

When the following adverse drug reactions occur, appropriate measures should be taken such as drug discontinuation depending on the symptom.

Capsules

	Frequency unknownNote)	≥0.5%
Skin	Rash, urticaria, erythema (including erythema multiforme), itching, haemorrhage subcutaneous	
Gastro-intestinal	Cheilitis/stomatitis (including ulcerative stomatitis), blood in stool, melaena, haematemesis, peptic ulcer	Abdominal pain (6.8%), diarrhea (5.5%), nausea (3.9%), vomiting, abdominal distension, feces abnormal, oral discomfort, anorexia
Psycho-neurological	Excitement, tremor, numbness, lethargy	Headache, somnolence, insomnia, vertigo
Circulatory	Supraventricular tachycardia, ventricular extrasystoles, electrocardiogram abnormal (ST elevated), palpitation	
Hepatic		AST (GOT) increased, ALT (GPT) increased, γ-GPT increased, Al-P increased
Renal	Haematuria	Proteinuria positive

Blood		Eosinophilia
Respiratory	Bronchitis, cough	
Eye	Eye abnormality (e.g. visual field disorders, vision blurred, diplopia, eye pain)	
Others	Fatigue, pyrexia, hypothermia, oedema	Blood glucose increased, back pain, chest pain

Dry Syrup

	Frequency unknown Note)	≥5%	<5%
Skin	Urticaria, erythema (including erythema multiforme), itching, haemorrhage subcutaneous		

	Frequency unknown Note)	≥5%	<5%
Gastro-intestinal	Cheilitis/stomatitis (including ulcerative stomatitis), blood in stool, melaena, haematemesis, peptic ulcer	Vomiting (24.3%), diarrhea (20.0%)	Loose stools, abdominal pain, nausea
Psycho-neurological	Lethargy		
Circulatory	Supraventricular tachycardia, ventricular extrasystoles, electrocardiogram abnormal (ST elevated), palpitation		
Hepatic		ALT (GPT) increased	AST (GOT) increased
Eye	Eye abnormality (e.g. visual field disorders, vision blurred, diplopia, eye pain)		
Others	Ear disorder (burning sensation, ear pain, etc.), conjunctivitis, pyrexia, hypothermia, oedema		Epistaxis

Note) The ADRs reported in Japanese and overseas clinical trials or in spontaneous reports for which frequencies can not be calculated are categorized as frequency unknown.

6. Pediatric Use
   (1) The safety of TAMIFLU in children under 1 year old (low birth weight infants, newborns, and nursing infants) has not been established (See “Other Precautions”).
   (2) TAMIFLU has not been administered to infants and children weighing less than 8.1 kg in overseas phase III clinical studies with TAMIFLU Dry Syrup.
7. Overdosage Up to the present, no adverse events due to overdose have been reported. However, in the phase I clinical studies of TAMIFLU Capsule conducted abroad in healthy adults, nausea, vomiting and dizziness have been reported at a dose of 200 mg or more.
8. Precaution concerning Use Precautions regarding dispensing: In the case of press-through package (PTP), instruct the patient to take TAMIFLU Capsules from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.]
9. Other Precautions
   (1) In the phase III prophylaxis study of TAMIFLU Capsule in Japan, one case of aggravated diabetes was reported. Furthermore, in the phase III prophylaxis study of TAMIFLU Capsule conducted abroad, 7 cases of aggravated diabetes or hyperglycemia were noted in subjects with glucose metabolism disorder. However, no inhibition of glucose metabolism was observed in non-clinical studies at a dose up to 100 times the clinical dose.
   (2) In the phase III treatment studies conducted abroad in the patients with chronic heart disease and chronic respiratory disease, no significant difference in the efficacy of TAMIFLU Capsule from the placebo was observed during the period of influenza symptoms. However, TAMIFLU significantly reduced the virus release duration. As a result, the duration required for recovery from fever, myalgia/arthralgia or rigors/sweating was significantly reduced.
   (3) In the phase III treatment studies of TAMIFLU Dry Syrup conducted abroad in children complicated with chronic asthma, the efficacy of TAMIFLU has not been verified. On the other hand, there was no noteworthy problem regarding the safety in this study.
   (4) In the phase III treatment studies of TAMIFLU Capsule conducted abroad in the elderly patients (65 years old or older), the treatment with TAMIFLU Capsule reduced the duration of influenza symptoms by about 50 hours (23%) in comparison with the placebo.
   (5) There has been no experience of repeated administration of TAMIFLU to the same flu patients during a given influenza season.
   (6) In the phase III prophylaxis study of TAMIFLU Capsule in Japan and abroad, there has been no experience of drug administration for more than 6 weeks.
   (7) In the toxicity study of single oral dose of TAMIFLU in juvenile rats (14 rats/group), death was observed in 3 and 2 pups dosed on Day 7 post-partum in the 1000-mg/kg and 700-mg/kg groups, respectively. On the other hand, no deaths were observed in pups dosed on Day 14 post-partum.
   (8) In the toxicokinetics study of single oral dose of TAMIFLU in juvenile rats, 1000 mg/kg of TAMIFLU was administered on Days 7, 14, 24 and 42 post-partum. Death was observed in 7/56 pups dosed on Day 7 post-partum, 1/28 pups dosed on Day 14 post-partum, but none in pups dosed on Day 24 and 42. The exposure levels of oseltamivir in the brain for rats Day 7 and 14 post partum were 1500-fold and 650-fold higher than Day 42 rats, respectively. However, oseltamivir exposure for rats dosed on Day 24 was only twice as high as that of Day 42.

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/s/

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