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

Date:	October 24, 2007
To:	Lisa Mathis, M.D., Associate Director Pediatric and Maternal Health Staff (PMHS) Office of New Drugs (OND), CDER M. Dianne Murphy, M.D., Director Office of Pediatric Therapeutics (OPT), OC
Thru:	Ann McMahon, M.D., MS, Deputy Director *For* Mark Avigan, M.D., C.M., Director Division of Drug Risk Evaluation Office of Surveillance and Epidemiology (OSE)
From:	Melissa M. Truffa, R.Ph. Safety Evaluator, Team Leader Division of Drug Risk Evaluation Office of Surveillance and Epidemiology (OSE)
Subject:	2- year Review of Pediatric Postmarketing Adverse Events (April 23, 2005 through May 31, 2007) and all Pediatric Deaths through May 31, 2007
Drug Name(s):	Tamiflu® (oseltamivir phosphate) Capsule and Oral Suspension
NDA Numbers:	NDA 21-087 and NDA 21-246
Date of Pediatric Exclusivity:	March 22, 2004
Applicant/sponsor:	Roche
OSE RCM #:	2007-2338

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EXECUTIVE SUMMARY

The one-year post pediatric exclusivity review for oseltamivir was completed on August 24, 2005 and covered the time period from March 22, 2004 through April 22, 2005. These data were presented at a November 2005 Pediatric Advisory Committee (PAC). Serious skin reactions and neuropsychiatric adverse events were two safety concerns highlighted at the 2005 PAC. Serious skin and hypersensitivity reactions were added to the **PRECAUTIONS** section of the Tamiflu label in December 2005 and neuropsychiatric events were added in November 2006. The 2005 committee members also requested an update of all pediatric adverse events following two additional influenza seasons (2005-06 and 2006-07). This review is response to the request for a 2-year update.

This review focuses on serious pediatric events that do not include a reported neuropsychiatric symptom received from April 23, 2005 to May 31, 2007 and all pediatric deaths through May 31, 2007. Neuropsychiatric adverse events particularly the reports of abnormal and impulsive behavior remain a safety concern and are discussed in detail under a separate cover.

Since the 2005 review there have been 13 additional pediatric deaths for a total of 25 reports of death in pediatric patients (ages 0-17 years) in the AERS database with the use of oseltamivir through May 31, 2007. Twenty-one are from Japan, three from the United States and one from Egypt (death from Avian influenza). These 25 reports include five deaths from traumatic injuries (considered related to neuropsychiatric adverse event), nine reports of sudden death (not considered related to neuropsychiatric adverse event), two deaths from complications of influenza, two deaths from cardio-pulmonary arrest, and one each from Avian influenza, acute pancreatitis, pneumonia, asphyxiation, possible encephalitis /cardiomyopathy, sepsis, and an unspecified death 8-9 months after receiving oseltamivir. The two deaths due to complications of influenza and the follow-up report of death from an unspecified reason in a female patient with co-morbidity that died 8-9 months after receiving oseltamivir are all from the United States.

The new reports since 2005 also include three deaths from traumatic injuries as a result of a possible neuropsychiatric adverse event (e.g. delirium), three pediatric deaths from sudden death and/or cardio-respiratory arrest (not considered related to a neuropsychiatric adverse event), one death from sepsis in an immunocompromised patient and one death from possible encephalitis/cardiomyopathy; all are from Japan.

In total there are five reported deaths from unusual traumatic injuries that are considered related to possible neuropsychiatric adverse event are all from Japan. The two most recent deaths in Japanese teenagers from February 2007 prompted the Japanese Ministry of Health, Labour and Welfare to restrict the use of oseltamivir in patients 10-19 years of age except in patients at increased risk from influenza-related complications. The nine reports of sudden death and/or cardiopulmonary arrest (not considered related to a neuropsychiatric adverse event) are also all from Japan. These nine reports are confounded by limited data and the complications of influenza.

As stated in previous reviews, it is still difficult to establish a direct causal relationship between the use of oseltamivir and the reported deaths because of confounding and

contributing factors (e.g. influenza) and limited data regarding the ability of oseltamivir and its metabolite to penetrate the CNS. However, the contribution of oseltamivir to some of these deaths, especially the five fatal reports from traumatic injuries, cannot be completely excluded based on the available information. Thus, DDRE will continue to closely monitor these events, but is not recommending any restrictions for the use of oseltamivir in U.S. pediatric patients at this time.

A review of unlabeled non-fatal serious adverse events (not including neuropsychiatric adverse events) with oseltamivir did not identify any new safety issues. However, the Division of Antiviral Products and the Division of Drug Risk Evaluation meet monthly during the influenza season to review adverse events reports with the four marketing antivirals for the treatment and prophylaxis of influenza. During the joint review from the most recent influenza season (2006-2007) we identified potential reports of bleeding abnormalities and visual disturbances with the use of oseltamivir. This prompted a detailed review of reports in all ages of bleeding abnormalities and visual disturbances in the AERS database to further investigate these potential safety signals; these reviews are currently ongoing.

1 TAMIFLU PRODUCTS, INDICATIONS, AND RELEVANT LABELING

1.1 TAMIFLU® PRODUCT FORMULATIONS

Tamiflu® Product Formulations					
NDA #	**Trade name**	**Dosage form**	**Approval date**	**Pediatric indication**	**Pediatric dose**
21-087	Tamiflu® (oseltamivir phosphate) Capsules	Capsule	10-27-99	Treatment and prophylaxis of influenza infection in patients 1 year and older	>40 Kg or >88 lbs: 75mg twice daily
21-246	Tamiflu® (oseltamivir phosphate) for Oral Suspension	Oral suspension	12-14-00	Treatment and prophylaxis of influenza infection in patients 1 year 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

1.2 RELEVANT PRODUCT LABELING FOR TAMIFLU® (OSELTAMIVIR)

PRECAUTIONS

Serious Skin/Hypersensitivity Reactions

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

Neuropsychiatric Events

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

2 AERS SEARCH RESULTS: TAMIFLU® (OSELTAMIVIR)

2.1 COUNT OF REPORTS: AERS SEARCH INCLUDING ALL SOURCES- U.S. & FOREIGN FROM MARKETING APPROVAL DATE (TABLE 1)

Table 1: Crude Counts[1] of AERS Reports for All Sources from Marketing Approval Date through May 31, 2007 (US counts in parentheses)

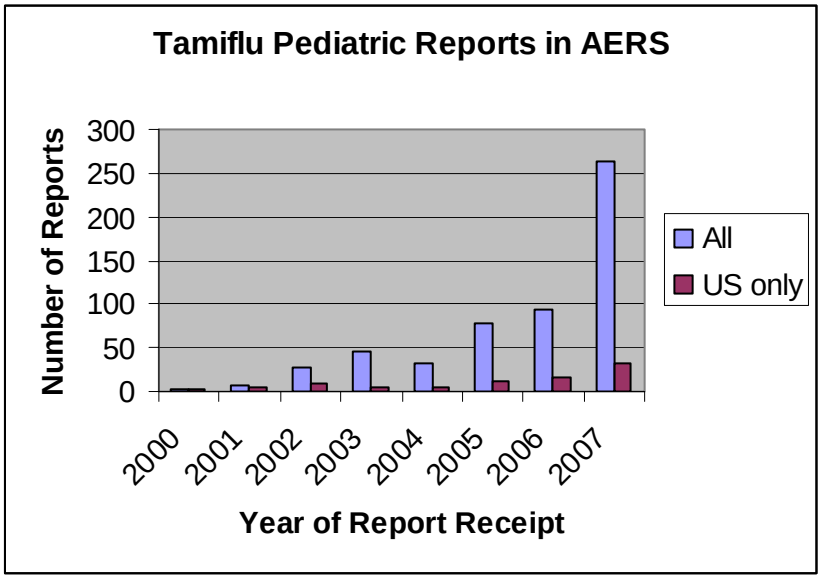
	All reports (US)	Serious[2] (US)	Death (US)
Adults (≥ 17 yrs.)	1254 (375)	1230 (352)	125 (36)
Pediatrics (0-16 yrs.)	550 (84)	546 (80)	25 (3)
Age unknown (Null values)	260 (214)	228 (182)	7 (4)
Total	2064 (673)	2004 (614)	157 (43)

[1] May include duplicates

[2] Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and medically significant.

- Approximately 15% of all pediatric reports in AERS are from the U.S.

Figure 1: Reporting Trend for Pediatric Reports for Oseltamivir (From approval date through May 31, 2007)



2.2 COUNT OF REPORTS: AERS SEARCH INCLUDING ALL SOURCES-U.S. & FOREIGN FROM APRIL 23, 2005 THROUGH MAY 31, 2007 (TABLE 2)

Table 2: Crude counts[1] of AERS Reports for All Sources from April 23, 2005 through May 31, 2007 (US counts in parentheses)

	All reports (US)	Serious[2] (US)	Death (US)
Adults (≥ 17 yrs.)	492 (67)	488 (63)	64 (9)
Pediatrics (0-16 yrs)	411 (55)	408 (52)	15 (3)
Age unknown (Null Values)	53 (28)	43 (18)	3 (2)
Total	956 (150)	939 (133)	82 (14)

[1] May include duplicates

[2] Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and medically significant.

- Approximately 13% of pediatric reports received from April 23, 2005 through May 31, 2007 are from the U.S.

3 POSTMARKETING REVIEW OF PEDIATRIC ADVERSE EVENTS WITH SERIOUS OUTCOME RECEIVED FOR TAMIFLU FROM APRIL 23, 2005 THROUGH MAY 31, 2007

3.1 CASE CHARACTERISTICS FOR PEDIATRIC CASES

3.1.1 Case Characteristics of All Pediatric Cases Received from April 23, 2005 through May 31, 2007 (Table 3)

3.1.2

Table 3: Characteristics of Pediatric Cases (Received April 23, 2005 through May 32, 2007) (N=410)*		
Gender	Male: Female: Not Stated:	259 143 8
Age	Mean= Median= 0-<1 month = 1 month - < 1 yr = 1-5 yrs = 6-11 yrs = 12-16 yrs = Not Stated =	9 years 8.7 years; (Range, 1 day-16 years) 2 12 104 149 135 8
Source	Japan: US: Other:	351 (86%) 54 (13%) 5 (1%))
Flu Season of Event Occurrence	2000-01 (1), 2001-02 (2), 2002-03 (6), 2003-04 (20), 2004-05 (59), 2005-06 (113), 2006-07 (184), Not stated (25)	
Outcomes	Death-15, Life-Threatening-44, Hosp-114, Disability-4, Congenital anomaly-1, Medically Significant-229, Not Stated-3	

*After removal of one duplicate report

3.1.3 Case Characteristics of Selected Pediatric Cases Received from April 23, 2005 through May 31, 2007 (Table 4)

Table 4 includes non-neuropsychiatric related pediatric cases; the focus of this review.

Table 4: Characteristics of Non-Neuropsychiatric Pediatric Cases (Received April 23, 2005 through May 32, 2007) (N=112)		
Gender	Male: Female: Not Stated:	50 59 3
Age	Mean= Median= 0-<1 month = 1 month - < 1 yr = 1-5 yrs = 6-11 yrs = 12-16 yrs = Not Stated =	6.6 years 5 years; (Range, 1 day-16 years) 2 7 47 30 23 3
Source	Japan: US: Other:	90 17 5
Flu Season of Event Occurrence	2001-02 (1), 2002-03 (1), 2003-04 (9), 2004-05 (32), 2005-06 (31), 2006-07 (23) and Not stated (15)	
Outcomes	Death-12, Life-Threatening-4, Hospitalization-30, Congenital anomaly-1, Medically Significant/Other-65	

3.2 ALL PEDIATRIC DEATHS (N = 25)

Since the 2005 review there have been 13 additional pediatric deaths for a total of 25 reports of death in pediatric patients (ages 0-17 years) in the AERS database listing oseltamivir as a suspect drug through May 31, 2007. Twenty-one are from Japan, three from the United States and one from Egypt (death from Avian influenza). The US cases include two deaths due to complications of influenza and a follow-up report of death from an unspecified reason in a female with co-morbidity that died 8-9 months after receiving oseltamivir. The new reports also include three deaths from traumatic injuries, three pediatric deaths from sudden death and/or cardio-respiratory arrest, one death from sepsis in an immunocompromised patient and one death from possible encephalitis/cardiomyopathy; all are from Japan.

Twelve pediatric deaths, all from Japan, were discussed at the November 2005 PAC. It was concluded at the time that based on available data, it is difficult to establish a direct causal relationship between the use of oseltamivir and the reported deaths because of confounding risk factors and limited follow-up data. Among the 12 cases there was one neuropsychiatric-related death in 14-yr-old who fell from the 9th floor of a building.

As of November 2006 we noted that 3 reported deaths in patients ≤17 year of age involved unusual traumatic injuries. We concluded that based on the available data, it is difficult to establish a direct relationship between the use of Tamiflu and these deaths; however, we were concerned about a potential pattern. Two additional deaths from traumatic injuries in Japanese teenagers (14 year-old female and 14-year-old male, respectively) occurred in February 2007 for a total of 5 pediatric deaths from Japan due to traumatic injuries (See Table 5, below). These deaths are considered part of a pattern related to the use of oseltamivir and its potential to cause neuropsychiatric adverse events. It should be noted that the two additional deaths from February 2007 prompted the Japanese Ministry of Health, Labour and Welfare (MHLW) to restrict the use of oseltamivir in patients 10-19 years of age.

Table 5: Deaths from Traumatic Injuries in Pediatric Patients Receiving Oseltamivir (N=5)

Case#	Event Year Location	Age (yrs) Sex	# Doses	Comment
4165603	2004 Japan	17 Male	1 dose	After 1 dose of Tamiflu jumped over concrete wall and leapt in front of truck; also received amantadine
5787263	2005 Japan	14 Male	1 dose	After 1 dose of Tamiflu fell off the 9th floor
6083411	2006 Japan	12 Male	1 dose	After 1 dose of Tamiflu found in parking lot presumably due to a fall.
6252128	2007 Japan	14 Female	1 dose	After 1 dose of Tamiflu rested at home; mother went out for groceries leaving patient alone. Within 3 hrs, she apparently fell from 1.4 meter high rail in front of the condo door to the 10th floor to the roof of a bicycle parking lot and then to the ground.

6252100	2007 Japan	14 Male	2 doses	After 2 doses of Tamiflu told mother he was going to restroom but instead opened front door and jumped over 1.26 meter high fence and leapt 30 meters from the 11th floor of the apartment. Died shortly afterwards from massive head injuries.

In addition to the 5 deaths from traumatic injuries there are nine reports of sudden death in pediatric patients; six from the initial review and 2005 presentation; and 3 new reports through May 31, 2007. These reports are described below in Table 6:

Table 6: Cases of Sudden Death in Pediatric Patients Receiving Oseltamivir (N=9)

Case#	Event Year Location	Age (yrs) Sex	Time to Event # Doses	Cause of Death/Comment
5758383	2002-03 JP	2 Male	1-2 days	Sudden Death/healthy male with influenza. Autopsy revealed brain and pulmonary edema.
5758385	2002-03 JP	2 Male	1-2 days	Sudden Death/male with asthma and influenza Autopsy results not released
5757451	2002-03 JP	3 Male	1-2 days	Sudden Death/healthy male with influenza. Autopsy results not released
5758389	2002-03 JP	3 Male	1-2 days	Sudden Death/asthma and influenza Autopsy revealed pulmonary edema.
3894346	2002 JP	2 Male	1 day	Sudden Death/male with influenza & mild "pseudo-croup" developed difficulty breathing, cardiopulmonary arrest and died. Encephalopathy & myocarditis suspected.
5770409	2005 JP	4 Female	1 day	Sudden Death/healthy female with influenza. One dose at night vomited; next morning notable cold feeling and pain in the limbs. 50 minutes later suddenly developed cardio-respiratory arrest and died.
5957314	2005 JP	7 Male	1 dose	Sudden Death/Down's syndrome; cough given epinephrine inhalation in ER; later developed difficulty breathing, at hospital cardio-pulmonary arrest was recorded
6274595	2007 JP	1.5 Female		Sudden Death/female with influenza; 4-6 hours after first dose developed respiratory arrest, artificial resuscitation was unsuccessful
6283605	2007 JP	3 Male	1 dose	Sudden Death/3.5 hours after first dose non-responsive, lying limply on his stomach not breathing and with no pulse. Cardiac resuscitation was unsuccessful.

The first four reports of "sudden death" described above are from a Japanese newspaper article concerning children that died suddenly in their sleep. These reports contained

limited data. Subsequent, literature reports[1,2] have proposed a causal association between the use of oseltamivir and sudden death; one such theory is based on the "sudden onset reactions related to central suppressive action of oseltamivir-P during cytokine storm". Another literature report[3] from AERS (submitted after May 31, 2007) describes a case of sudden death and pulmonary edema in 3-year-old Japanese patient and the reporter states "It appears that in a state of hypoxia, the epithelial Na channels and Na+/K+-Aptase are down regulated, thus inducing pulmonary edema, but these symptoms are fully reversible by reoxygeneration. Pulmonary edema in cases of sudden death following oseltamivir administration is attributed to respiratory inhibition by oseltamivir and irreversible blood hypoxia." Although there is some data from animal studies to suggest that oseltamivir and its metabolite affect the CNS of juvenile rats. It is difficult to extrapolate meaningful data from juvenile rats to human pediatric patients and these data are considered inconclusive.

As previously stated, it is still difficult to establish a direct causal relationship between the use of oseltamivir and the reported deaths because of confounding and contributing factors (e.g. influenza) and limited data. However, the contribution of oseltamivir in some of these deaths, especially the five fatal reports from traumatic injuries (considered related to a potential neuropsychiatric adverse event), cannot be completely excluded based on the available information.

A description of the 25 pediatric deaths can be found in Appendix 1 (Table 7).

Reviewer Comment: Two additional deaths from Japan were received after the May 31, 2007 cut-off date in this review. A report of GI bleed in 8-yr-old with chronic ulcers that was considered unrelated to the use of oseltamivir and report of sudden death and pulmonary edema in 3-yea- old that is described above from a literature report.

3.3 SUMMARY OF NON-FATAL SERIOUS CASES OTHER THAN NEUROPSYCHIATRIC EVENTS [RECEIVED FORM APRIL 23, 2005 THROUGH MAY 31, 2007 BY PRIMARY ADVERSE EVENT DESCRIBED IN NARRATIVE (N = 100)]

3.3.1 UNLABELED EVENTS

Bleeding events (n=17)

The majority of the reports are for bloody diarrhea (n=2) or melena with or without diarrhea (n=5). There are also three reports of hematemesis and one report each of gingival bleeding; hematuria or chromaturia that was not medically confirmed; and eye hemorrhage with epistaxis, melena and diarrhea. Finally, we noted 4 reports of decreased

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[1] Hama, R. Fifty Sudden Deaths may be Related to Central Suppression. BMJ 2007;335:59 (14 July)

[2] Hama, R. Limited Benefit and Potential Harm of Oseltamivir including Sudden Death and Death from Abnormal Behaviour. www.bmj.com/cgi/eletter/331/7526/1203-b#122513

[3] Hama, R. Discussion of Causal Relationship between Oseltamivir and Sudden Death During Sleep in Two Autopsy Cases. Journal of Japanese Pediatric Society (2007.4.20, 21, 22) 111 (2) 209/(2007.2)

platelets. Two had no clinical signs or symptoms of bleeding; the other two reported epistaxis and petechiae with the latter case requiring a platelet transfusion**.**

Reviewer Comment: It should be noted that during routine monitoring of adverse events with oseltamivir during the last influenza season (2006-2007) reports of serious bleeding abnormalities were identified as a potential safety signal. This prompted a detailed review to further evaluate this potential signal in patients of all ages that is currently ongoing.

Hypothermia (n=14)

Thirteen reports of non-serious "hypothermia" after the use of Tamiflu in pediatric Japanese patients with influenza including one serious report of hypothermia in a 4-year-old that required hospitalization and treatment with heating blanket and fluid replacement. The patient was prescribed oseltamivir and acetaminophen for the treatment of influenza B. On the 5th day his body temperature decreased from 35.4 to 34.4 degrees Celsius. He was hospitalized and treated. The patient's temperature rapidly increased and he was discharged the next day.

Reviewer Comment: In the vast majority of patients hypothermia was diagnosed based on decreases in body temperature below 35 degree Celsius without clinical symptoms. Patients rapidly recovered without treatment. Many of these patients were also receiving concomitant antipyretics. No labeling changes are recommended at this time.

Medication Errors/Overdose (n=6)

Five of the reports are from U.S. and one is from Japan. A 4-month old male accidentally received 60 mg of oseltamivir daily for 5 days and experienced diarrhea, wheezing, fever and ear infection. A one-year-old Japanese patient was accidentally prescribed 10 times the recommended dose. She experienced vomiting and somnolence and required a gastric lavage; no other adverse effects were noted. Three additional patients experienced dosing errors because of confusion with teaspoons and milliliters. Two patients did not experience any adverse effects after receiving the incorrect dose; one patient experienced vomiting and hallucinations. The remaining patient was accidentally given an overdose of Seroquel (quetiapine) by a caregiver instead of the prescribed oseltamivir.

Reviewer Comment: The Division of Medication Errors completed a review of medication errors with oseltamivir in September 2006. One of DMETS recommendations was for the sponsor to develop a dosing syringe that measures in milliliters in order to alleviate confusion in dosing of Tamiflu Oral suspension. This would give pharmacists a tool to aid patients /caregivers in the most accurate dosing of Tamiflu.

Muscle Weakness (n=3)

There is one report each for rhabdomyolysis (CPK of 907, units not specified), myositis, and painful myalgia of lower extremities, respectively, in 3 pediatric patients being treated for influenza with oseltamivir. All three reporters stated that these adverse events could also be attributed to influenza.

Reviewer Comment: Myositis, rhabdomyolysis, and myoglobinuria are occasional complications of influenza infection. Although myalgias are exceedingly common in

influenza, true myositis is rare. Patients with acute myositis have exquisite tenderness of the affected muscles, most commonly in the legs, and may not be able to tolerate even the slightest pressure, such as the touch of bedsheets. Serum levels of creatine phosphokinase and aldolase are markedly elevated, and an occasional patient has developed renal failure from myoglobinuria. The pathogenesis of influenza-associated myositis is also unclear, although the presence of the influenza virus in affected muscles has been reported[4]. No labeling changes are recommended at this time. DDRE will continue to monitor for reports of severe muscle weakness with oseltamivir.

Congenital Anomaly (n=3)

Three reports of congenital anomalies in infants born to pregnant women receiving oseltamivir. The first report is a case of ventricular septal defect in an infant born to a mother who received 5 days of oseltamivir for treatment of influenza during the 6th week of pregnancy. The second report is in a 25-year-old pregnant female who received oseltamivir during the 6th week of pregnancy for treatment of influenza. Approximately 7 weeks later the fetus was diagnosed with "hydrop fetalis due to isoimmunization"; one month later the fetus died in uterus. The final report is a case of anophthalmos. Mother took oseltamivir during the 5-6 weeks of pregnancy for treatment of influenza. All three reports are from Japan and two are from a study, ML16864 (a protocol of special surveillance of Tamiflu capsules 75 mg in pregnant women and women who have just given birth).

Reviewer Comment: All three events occurred after maternal exposure to oseltamivir at 5-6 weeks of gestation. All three patients had influenza. There is no clear pattern to the events reported. Recommendation to request the protocol and study results from the sponsor for review.

Hematological Events (n=3)

There is one report each of pancytopenia, neutrophils count decreased and leucopenia in Japanese pediatric patients being treated for influenza. The report of pancytopenia was considered as possibly due to paravirus by the reporter, and the patient with decreased neutrophils had juvenile rheumatoid arthritis and was on concomitant aspirin. These appear to be reports of laboratory abnormalities without significant clinical symptoms and all three patients recovered within a few days.

Reviewer Comment: Based on the review of these cases with limited data no labeling changes or further actions are recommended at this time. DDRE will continue to monitor for hematological events.

Renal Toxicity (n=2)

There is one report of renal tubular necrosis and two report of nephrotic syndrome. The patient with renal tubular necrosis experienced decreased urine output and edema and suspected nephritic syndrome prior to starting treatment with oseltamivir. Oseltamivir is renally excreted and may have exacerbated the pre-existing renal insufficiency. A 3-year-old male with suspected influenza developed facial edema on the second day of

[4] **Harrison's Principles of Internal Medicine - 16th Ed. (2005)**

therapy with oseltamivir. Swelling increased 2 days after completing a 5-day course of oseltamivir and nephrotic syndrome was diagnosed. The reporter initially considered the nephrotic syndrome to be drug-induced; however, the event persisted after oseltamivir was discontinued and the reporter suspected that it was due to infection rather than drug-induced.

Reviewer Comment: *Renal toxicity was evaluated in a review dated December 2005. The executive summary states "A search of FDA's Adverse Event Reporting System (AERS) identified 21 cases of hepatic toxicity (including 14 cases of hepatic failure) and 43 cases of renal toxicity (including 18 cases of renal failure) with a serious outcome. These cases are confounded by other risk factors and concomitant medications and no sentinel case of liver or renal toxicity was identified in these case series that can be solely related to oseltamivir. Because a clear association could not be determined based upon the current case series, we do not recommend that hepatic failure/fulminant hepatitis or renal failure/impairment be added to the oseltamivir label at this time. We will continue to monitor postmarketing cases and discuss with DAVP in a timely manner as reports become available."*[5] *Based on the review of these cases with plausible alternative explanations for the renal toxicity no labeling changes are recommended at this time. However, we will continue to monitor postmarketing cases and discuss with DAVP in a timely manner as reports become available.*

Visual Disturbances (n=2)

There is one report each of diplopia and difficult focusing eye in a 12-year-old female and 14-year-old male, respectively. The 12-year-old reported blurred vision and diplopia after two doses of oseltamivir; the adverse events resolved after discontinuation of Tamiflu. Six days after the 14-year-old male completed a 5 day course of oseltamivir for influenza he developed "difficulty focusing eyes". His symptoms were not improving approximately a week later; he consulted an otology clinic and not abnormalities were noted and his MRI was also normal. The symptoms resolved approximately 18 days after onset. The patient had no adverse reactions after previous exposure to Tamiflu one or two years ago.

Reviewer Comment: It should be noted that during routine monitoring of adverse events with oseltamivir during the last influenza season (2006-2007) reports of visual abnormalities with a temporal association to the use of oseltamivir were identified as a potential safety signal. This prompted a detailed review to further evaluate this potential signal in patients of all ages that is currently ongoing.

Hepatic Events (n=7)

There are 5 reports of abnormal hepatic function with increased liver function tests. Jaundice was not reported and four of the five patients stated that the abnormal hepatic function resolved. The 4th case was persisting at the time of the report but there is no

[5] Post-Marketing Adverse Event Reports Review of serious skin/soft tissue disorders, anaphylaxis, renal toxicity, hepatic toxicity, and central nervous system/psychiatric disorders associated with the use of Tamiflu®. December 16, 2005.

follow-up information. There is also one report each of hepatitis and hematomegaly with hypothermia.

Reviewer Comment: Hepatitis and liver function tests abnormal are listed in the ***Observed During Clinical Practice*** *section of the Tamiflu label. Based on the review of these cases of increased liver function tests that resolved no additional labeling changes are recommended at this time. However, we will continue to monitor postmarketing cases and discuss with DAVP in a timely manner as reports of severe or acute liver toxicity become available." It should also be noted that hepatotoxicity was evaluated in a review dated December 2005. The executive summary states "A search of FDA's Adverse Event Reporting System (AERS) identified 21 cases of hepatic toxicity (including 14 cases of hepatic failure) and 43 cases of renal toxicity (including 18 cases of renal failure) with a serious outcome. These cases are confounded by other risk factors and concomitant medications and no sentinel case of liver or renal toxicity was identified in these case series that can be solely related to oseltamivir. Because a clear association could not be determined based upon the current case series, we do not recommend that hepatic failure/fulminant hepatitis or renal failure/impairment be added to the oseltamivir label at this time. We will continue to monitor postmarketing cases and discuss with DAVP in a timely manner as reports become available."*[6]

Miscellaneous (n=17)

The following adverse events occurred with a frequency of one or were present prior to starting therapy with oseltamivir. It is difficult to attribute causality to treatment with oseltamivir considering the limited data and plausible alternative explanations for the event: Impaired hearing- 1, interstitial pneumonia and atelectasis-1, hypoproteinemia and hypercholesterolemia-1, cardio-respiratory arrest with possible encephalopathy-1, salivary hypersecretion and expressive language disorder-1, tremor-1, intestinal obstruction-1, conduction disorder in patient with Wolff-Parkinson-White syndrome-1, fontanelle bulging in 5 month-old patient-1, myoclonus-1, drug reistance-1, cerebral infaction-1, acute encephalopathy-1, chromaturia, transient increase in coagulation factor VII and vascular purpura-1, and disseminated intravascular coagulation (DIC) in a newborn (see description of case below)-1.

Disseminated Intravascular Coagulation: DIC was reported in a newborn after maternal exposure to oseltamivir. The mother was diagnosed with influenza and received two doses of oseltamivir. On the same day the mother delivered a male infant by cesarean section because of membrane rupture. The baby had subcutaneous bleeding and decreased platelet count. The patient was treated with heparin and platelets and improved. The reporter commented that there was "little relationship between DIC in the patient and the use of Tamiflu by the mother."

3.3.2 LABELED EVENTS

[6] Post-Marketing Adverse Event Reports Review of serious skin/soft tissue disorders, anaphylaxis, renal toxicity, hepatic toxicity, and central nervous system/psychiatric disorders associated with the use of Tamiflu®. December 16, 2005.

Hypersensitivity/Serious Skin Reactions (n= 24)

Twenty-three postmarketing report of serious skin and hypersensitivity reactions were identify during this review. Serious skin and hypersensitivity reactions were added to the **PRECAUTIONS** section of the Tamiflu label in December 2005. No additional updates to the Tamiflu® label are recommended at this time.

GI symptoms (n=2)

There is one report each for vomiting and diarrhea with oseltamivir; both of which are labeled events.

4 SUMMARY

Since the 2005 review there have been 13 additional pediatric deaths for a total of 25 reports of death in pediatric patients (ages 0-17 years) in the AERS database with the use of oseltamivir through May 31, 2007. Twenty-one are from Japan, three from the United States and one from Egypt (death from Avian influenza). Of note are the five reported deaths from unusual traumatic injuries considered related to neuropsychiatric adverse event (e.g. delirium) and nine reports of sudden death (not considered related to neuropsychiatric adverse event); all are from Japan. As stated in previous reviews, it is still difficult to establish a direct causal relationship between the use of oseltamivir and the reported deaths because of confounding and contributing factors (e.g. influenza) and limited data regarding the ability of oseltamivir and its metabolite to penetrate the CNS. However, the contribution of oseltamivir to some of these deaths, especially the five fatal reports from traumatic injuries, cannot be completely excluded based on the information available. Therefore, DDRE will continue to closely monitor these reports, but we are not recommending any restrictions for the use of oseltamivir in U.S. pediatric patients at this time.

Renal and hepatic toxicity in all patients were reviewed in December 2005 and no sentinel case of liver or renal toxicity was identified in the case series that can be solely related to oseltamivir. We will continue to monitor postmarketing cases and discuss with DAVP in a timely manner as serious reports of renal or hepatic failure become available.

A review of unlabeled non-fatal serious adverse events (not including neuropsychiatric adverse events) with oseltamivir did not identify any new safety issues. However, the Division of Antiviral Products and the Division of Drug Risk Evaluation meet monthly during the influenza season to review adverse events reports with the four marketing antivirals for the treatment and prophylaxis of influenza. During the joint review from the most recent influenza season (2006-2007) we identified potential reports of bleeding abnormalities and visual disturbances with the use of oseltamivir. This prompted a detailed review of reports in all ages of bleeding abnormalities and visual disturbances in the AERS database to further investigate these potential safety signals; these reviews are currently ongoing.

Appendix 1

Table 7: Deaths in Pediatric Patients (0-17 years) receiving oseltamivir in AERS through May 31, 2007 (N= 25)							
	MFR #	**AERS #**	**Age/Sex**	**Date/Loc.**	**Event**	**Duration**	**Concomitant Meds**
1	JP-Roche-398613	5826323	4 M	2005 Japan	Cardio-respiratory arrest\, Anaphylactic shock, Brain death, Increased myoglobin, Increased CPK	3 days	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	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	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	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 two days after starting therapy with oseltamivir for the treatment on influenza A during the 2002-2003 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.							

Table 7: Deaths in Pediatric Patients (0-17 years) receiving oseltamivir in AERS through May 31, 2007 (N= 25)							
	MFR #	**AERS #**	**Age/Sex**	**Date/Loc.**	**Event**	**Duration**	**Concomitant Meds**
5*	JP-Roche-397182	5758385	2 M	2002-2003 Japan	Sudden death	1-2 days	Unknown
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 two days after starting therapy with oseltamivir for the treatment on influenza A during the 2002-2003 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	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 two days after starting therapy with oseltamivir for the treatment on influenza A during the 2002-2003 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	1-2 days	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 2002-2003 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	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 improved 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.							

Table 7: Deaths in Pediatric Patients (0-17 years) receiving oseltamivir in AERS through May 31, 2007 (N= 25)							
	MFR #	**AERS #**	**Age/Sex**	**Date/Loc.**	**Event**	**Dose/Duration**	**Concomitant Meds**
9	JP-Roche-403186	5787263	14 M	Feb 2005 Japan	Abnormal behavior, depressed level of consciousness, fall, hemorrhagic shock	1 dose	None reported
On the morning of 5 Feb 2005 the patient visited a clinic and complained of fever, arthritic and pharyngeal pain. Diagnostic test from nasal cavity was positive for influenza A. No disturbed consciousness or mental symptoms were present. At 4pm the patient took one capsule of Tamiflu. 2 hours later at 6pm the patient fell off his apartment on the 9th floor onto the ground. At 11pm the patient died due to hemorrhagic shock at the hospital. No autopsy was performed. Treating Physician's comment is as follow. "The drug that the patient took before his death was only one capsule of Tamiflu. Because no one witnessed the circumstances of the fall, and it is not clear whether the patient was having disturbed consciousness or mental disorder. It may be safe to say that taking Tamiflu may have been related to the event. Influenza encephalopathy may be another possible contributing factor."							
10	329358	3894346	2 M	2002 Japan	Sudden Death, cardio-pulmonary arrest, Myocarditis	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 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	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	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.							

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	MFR #	**AERS #**	**Age/Sex**	**Date/Loc.**	**Event**	**Dose/Duration**	**Concomitant Meds**
13	CTU 263413E US-Roche-428129	5928974 5947635	3 F	2005 US	Sudden death, mental status changes, respiratory arrest, pneumonia strep	5 days	APAP, ibuprofen
I read a release today reporting on possible side effects of Tamiflu in children. In late January of 2004 my 3 year old daughter contracted flu. She was treated with Tamiflu and subsequently died 5 days later. She died suddenly in our bed several hours before we were taking her back to her pediatrician to be checked. She manifested some of the same symptoms -altered mental status- that are mentioned in the Tamiflu release. To this day, no one truly understands why she died. We contacted experts at the CDC who stated even they do not understand why some children react to the flu. Emily was found to have a severe strep pneumonia infection in her left lung -also unexplained how it set in so quickly-. They did not indicate any involvement in her brain; although I am not sure they really looked during the autopsy. She was normal healthy child and that would explain why she succumbed to the flu. I never thought to consider whether the Tamiflu might have caused this until I saw the release and recognized some of the same symptoms and unusual circumstances with Emily's death. Although she stopped breathing at our house, they were able to get her heart started at the hospital, but she never recovered brain function. I have her complete medical record if necessary. Follow-up request.							
14	JP-Roche-429933	5957314	7 M	Dec 2005 Japan	Sudden death, GI hemorrhage, dyspnea, cardio-pulmonary arrest	1 dose	
Patient with Down's syndrome received Tamiflu and experienced sudden death and GI hemorrhage. On 14 DEC 2005, around noon, fever developed; influenza was diagnosed the next day and Tamiflu was prescribed. Around 5pm on 12/15 the patient took a dose of Tamiflu. On Dec 16th he visited the ER for cough. EPINEPHRINE inhalation was given and he was sent home. Later that evening he had difficulty breathing and was instructed to go to hospital; however, his breathing stopped and an ambulance was called. Upon arrival at hospital cardio-pulmonary arrest was recorded and IV epinephrine was administered. There was blood in his stool in his diaper and some bloody objects in stomach contents were also found. The patient was given CPR but died. Autopsy results = unknown.							
15	JP-Roche-453977	6083411	12 M	July 2006 Japan	Cardio-pulmonary arrest, fall, hemorrhage, pelvic fracture, multiple fractures	1 dose	Acetaminophen
3 Jul 2006: Patient with almost 40 degree C temperature in the morning and stayed home from school. Around noon he took 1 capsule of Tamiflu that has been prescribed to his brother on 310Jun06. Around 3pm, APAP was administered because he was still febrile. Around 6pm the brother noticed that he was gone and there was a call to the police that the patient was laying on the ground in the parking lot of a high-rise apartment building. He was in cardio-pulmonary arrest upon arrival at the hospital with injuries (multiple fractures) presumed due to a fall. Resuscitation was continued but the patient died at 7:05 pm. Autopsy revealed that he died from the hemorrhage from the pelvic fracture. It was assumed that he fell from the high-rise apartment building for some reason.							
16	JP-Roche-438133	5998635	3 M	Feb 2006 Japan	Cardio-pulmonary arrest Cardiomyopathy Encephalitis	1 dose	Ventalin, Berachin, Pulsmarin A, Anhiba, Bosmin

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(N= 25)

Patient diagnosed with Influenza A and started oseltamivir syrup. The next day he was hospitalized for cardio-pulmonary arrest and died. No autopsy was performed. Death possibly due to influenza encephalopathy or cardiomyopathy. No convulsions, disturbed consciousness of abnormal behavior.

	MFR #	AERS #	Age/Sex	Date/Loc.	Event	Dose/Duration	Concomitant Meds
17	US-Roche-450783	6066687	8 F	Jan 2002 US	Anxiety, depression, SJS, TEN		Ibuprofen, diphenhydramine, Klonopin, Ambien
An 8-year-old female patient died after experiencing SJS, TEN, depression, and anxiety after the use of oseltamivir and ibuprofen. The child spent 110 days in 4 different hospitals and near death several times. She was wheel chair bound, blind, and spoke with an electric pharynx. The mother had a history of allergies (hives) and the patient had been previously treated with ibuprofen. The patient started oral ibuprofen every 4-5 hours around the clock and oseltamivir on 06 Apr 2002. The next day a rash was noted and diphenhydramine was started. Oseltamivir was discontinued. The next day the patient had oral blisters and conjunctivitis. She was admitted to the hospital with diagnosis of SJS and TEN. On 09 April 06, ibuprofen was discontinued and the next day the patient developed acute respiratory syndrome and several secondary infections, including fungemia, She also experienced palatal adhesions, obstructive jaundice, corneal synecheal, pneumothorases with chest tube placement and required pressor support. The patient developed depression and anxiety which was treated with clonazepam and zolpidem. The patient underwent extensive rehabilitation. The patient died from unstated reasons on 17 Dec 2002, 8 months after receiving oseltamivir.							
18	US-Roche-482751	6241452	16 F	Mar 2007 US/TX	Aggression, DIC, influenza	3 days	Not stated
Newspaper article: Patient totally healthy with no underlying health issues. Positive Influenza A test; started oseltamivir. Over the next few days the patient developed pneumonitis and her general condition worsened with increased cough, chills, fever, and lethargy and combativeness. Patient admitted to the hospital, rapid influenza test negative after being on oseltamivir for 82 hours. Subsequently, the patient developed DIC and died 9 days later after starting Tamiflu.							
19	EG-Roche-477953	6214246	16 F	Jan 2007 Egypt	Avian Influenza	4 days	amantadine
Patient developed symptoms of Avian influenza and did not report it. 2-3 days later 13 out of 17 ducks died and 3 ducks were slaughtered. The patient was involved in defeathering the ducks. Patient admitted to the hospital and received 2 doses of amantadine and denied any exposure to dead birds. Received empirical treatment without any testing for influenza. Oseltamivir was started the next day and patient tested positive for H5N1. Patient's father admitted for the first time that the patient had been in contact with slaughtered ducks. Patient died 6 days after hospitalization of Avian flu.							
20	JP-Roche-484906	6252100	14 M	Feb 2007 Japan	Abnormal behavior, traumatic head injury	2 dose	APAP
Patient presented with fever (38.9 degrees C) Positive for Influenza B. Tamiflu for 5 days and APAP for 3 days were prescribed. A second dose of Tamiflu was given at 6:30 and later that night the patient woke-up and complained that he felt ill. His mother tried to give him another tablet but decided against it because less than 8 hours had passed since he took his last dose of Tamiflu. Shortly after he told his mother that he was going to the restroom but instead he opened the front door to go outside and jumped over a 1.26 meter high fence and leapt 30 meters from the 11th floor of the apartment. He died shortly afterwards from massive head injuries. No suicide note.							

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	MFR #	**AERS #**	**Age/Sex**	**Date/Loc.**	**Event**	**Dose/Duration**	**Concomitant Meds**
21	JP-Roche-483425	6252128	14 F	Feb 2007 Japan	Fall, death unexplained	1 dose	Other medications not specified
Feb 16th: Patient stayed away from school because of high-grade fever due to influenza. Influenza was diagnosed and several drugs including oseltamivir were prescribed. She went home and according to parents looked concerned that she might miss the final examinations scheduled for Feb 19th. Patient took Tamiflu and rested at home; the mother went out for groceries and the patient was alone at the time. Within less than 3 hours, she apparently fell from the 1.4 meter high rail in the hallway in front of the condo door to the 10th floor to the roof of a bicycle parking lot and then to the ground. A resident of the first floor found her lying and bleeding near the building and called an ambulance. She was wearing black sweatshirt and pants and no shoes on her feet. She had hit her head and body severely. About one hour after being transferred to the hospital, she died of traumatic shock; no suicide note has been found. No autopsy was performed. Patient was talking to her mother 1-2 hours before the incident and she looked no different than any other day.							
22	JP-Roche-489395	6274595	1.5 F	Feb 2007 Japan	Cardio-respiratory arrest	1 dose	Erythrocin. Dexchlorpheniramine, Mucosal (ambroxol), tipepidine hibenzate, tulobuterol
Patient developed fever, cough and nasal discharge. Influenza test was negative; bronchitis was suspected and patient prescribed antibiotics and placed under observation. Fever persisted and a return visit to clinic showed a **positive influenza test.** Tamiflu was prescribed and the patient took one dose. 4-6 hours later patient developed respiratory arrest. Artificial resuscitation was performed but was unsuccessful and the patient died. No autopsy.							
23	JP-Roche-490644	6280751	6 M	Mar 2007	Encephalitis Sepsis	Multiple doses	Fluconazole, Cytarabine, Novantron, Antineoplastic NOS
6 yr old immunocompromised patient after chemotherapy for AML received oseltamivir for influenza prophylaxis. While receiving oseltamivir the patient developed bacterial meningoencephalitis and sepsis. He subsequently died. Autopsy performed; no results reported.							
24	JP-Roche-491732	6283605	3 M	Mar 2007 Japan	Cardio-respiratory arrest Death	1 dose	None stated
Patient developed a fever and diagnosed with influenza A. He received his first dose of oseltamivir and 3.5 hours later was non-responsive, lying limply on his stomach not breathing and with no pulse. Cardiac resuscitation was unsuccessful and the patient died. No autopsy was preformed.							
25	JP-Roche-372431	4165603	17 M	Feb 2004 Japan	Abnormal behavior, chest injury, completed suicide, road traffic accident, shock,	1 dose	Amantadine, Pasetocin, Dasen, Mucosolvan

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17 yr old male with a fever was diagnosed with influenza A and prescribed Tamiflu. During his clinic visit his mental status was normal. He was sent home and instructed to stop his amantadine (which he was taking for influenza prophylaxis) and start Tamiflu after lunch. His last amantadine dose was the morning of his clinic visit. 90 minutes after one dose of Tamiflu the patient awoke from a nap, ran out without shoes, through the snow, and jumped over a concrete wall. He crossed the railroad and went over a guard rail onto the National Highway and leapt in front of a truck. The patient died due to traumatic chest injuries. No autopsy was performed. The patient did not have a history of psychiatric problems. It is unknown if was taking other medications, health foods, or herbal medicines at the time of the incident.

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

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