

Postmarketing Safety Update for Influenza Antivirals

Pediatric Advisory Committee Meeting November 27, 2007

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Overview

- Adverse Event Reporting System (AERS)
- Tamiflu® Safety Update
 - Drug Use Data
 - Pediatric Death Reports
 - Neuropsychiatric Events
- Neuropsychiatric Reviews:
 - Relenza™ (zanamivir)
 - Symmetrel® (amantadine HCl)
 - Flumadine® (rimantadine HCl)
- DDRE Conclusions & Recommendations



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AERS Database Overview

- Adverse Event Reporting System (AERS)
- Voluntary, “spontaneous” reporting system
 - Sponsors required to report (21CFR314.80)
- Computerized database
- Origin 1969; > 3 million reports
- Contains human drug and “therapeutic” biologic reports



AERS Strengths

- Includes all U.S. marketed products
- Simple, inexpensive reporting system
- Detection of events not seen in clinical trials (“signal generation”)
- Especially good for events with rare background rate, short latency
- Case series evaluation: identification of trends, drug indication, population, and other clinically significant emerging safety concerns



AERS Limitations

- Extensive underreporting
- Reporting biases
- Actual numerator (# of events in population) & denominator (# of exposed patients in population) not known
- Quality of report is variable (foreign reports subject to translation)
- Duplicate reporting occurs
- Difficult to attribute events with a high background rate, confounders, long latency



Influenza Products - Enhanced Monitoring

During flu season (October-April):

- Safety Evaluator prepares monthly summary of neuropsychiatric events for oseltamivir, zanamivir, amantadine, or rimantadine
- OSE and DAVP meet monthly to discuss these reports and identify any new safety signals.
- If a new safety signal or change in reporting of a labeled serious adverse event is identified, a formal review of AERS is initiated by OSE.
- U.S. Prescription Use Data is also reviewed during these meetings to identify any trends



Tamiflu[®] (oseltamivir) Safety Update

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Oseltamivir - Background

- **Drug:** Tamiflu[®] (oseltamivir phosphate) oral capsules and suspension
- **Therapeutic Class:** Neuraminidase inhibitor
- **Sponsor:** Hoffmann-La Roche Inc.
- **Indications:**
 - Treatment of influenza (≥ 1 yr)
 - Prophylaxis of influenza (≥ 1 yr)
- **Pediatric Exclusivity:** granted March 22, 2004



Oseltamivir - U.S. Labeling (updated November 2006)

PRECAUTIONS - *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.



Oseltamivir-Warning in Japanese PI:

Although the causal relationship is unknown there have been reports of the development of abnormal behaviour leading to an accidental fall after taking Tamiflu in patients aged from 10 to 19 years old. Therefore, patients in this age group should refrain from using Tamiflu, in principle, excluding patients at high risk from complications, medical history, etc. For children and teenagers, in order to prevent the remote chance of an accident occurring after the start of Tamiflu treatment, patients and the family should be well informed on 1) the potential for developing abnormal behaviour, and 2) guardians should take care not to leave a child or teenager patients alone at least for 2 days when treated at home.

Furthermore, similar symptoms may occur for influenza encephalopathy, etc., therefore, the same explanation as the above should be provided



Oseltamivir – European Labeling

Undesirable Effects

- Convulsions and psychiatric events such as depressed level of consciousness, abnormal behavior, hallucinations and delirium have been reported during Tamiflu administration. In rare cases, the delirium resulted in accidental injury. The symptoms were mainly reported in children and adolescents. Convulsions and psychiatric symptoms have also been reported in patients with influenza not taking Tamiflu.

Package Leaflet

- Convulsion, depressed level of consciousness, abnormal behavior, hallucinations and delirium have been reported during Tamiflu administration, leading in rare cases to accidental injury. Patients, especially children and adolescents, should be closely monitored and their healthcare professional should be contacted immediately if the patient shows any signs of unusual behavior.

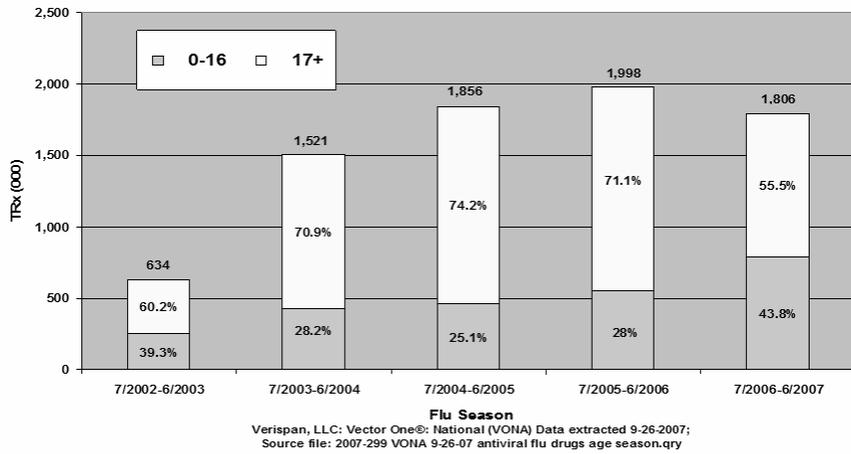


Tamiflu[®] (oseltamivir) Update:

Drug Use Data

Oseltamivir - Drug Use Data

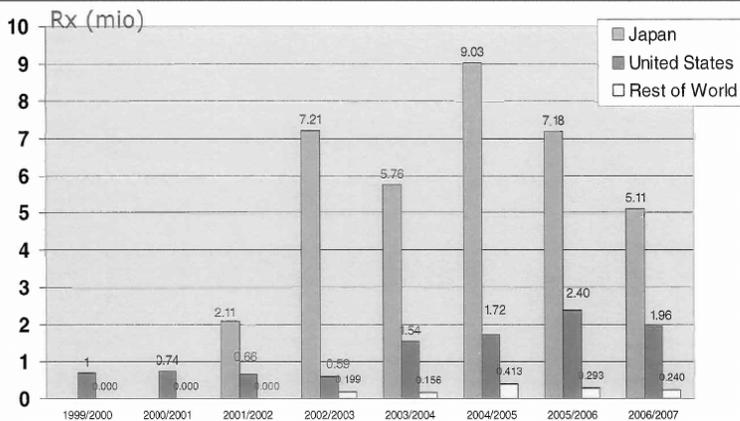
Total Number of Tamiflu Prescriptions (in thousands) Dispensed from U.S. Retail Pharmacies by Age (July 2002-June 2007)



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Tamiflu® Prescriptions by Season and Country All Ages

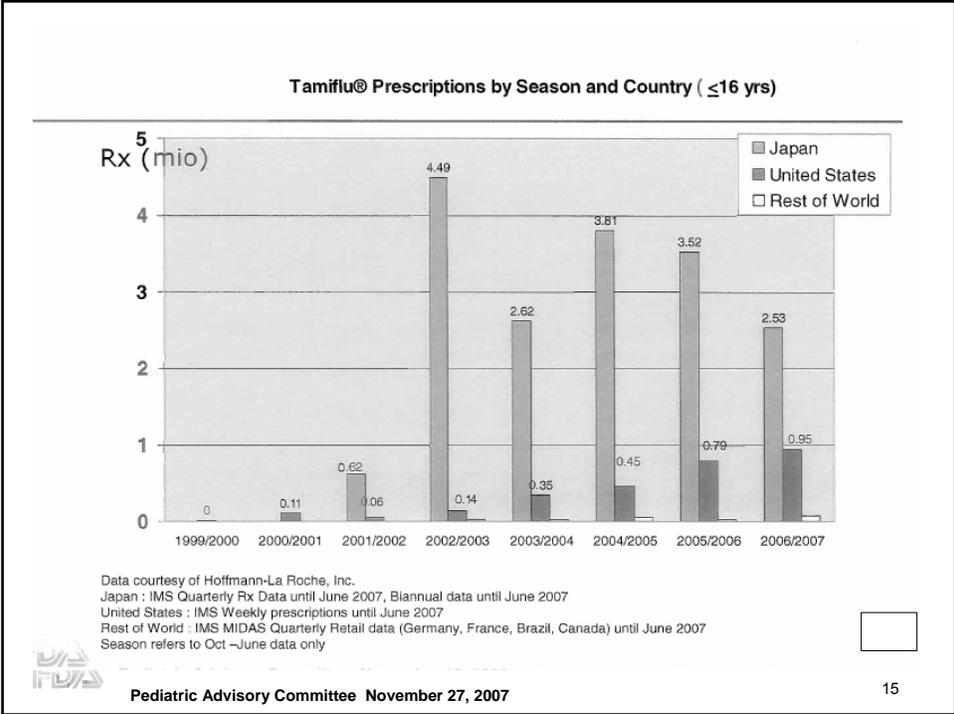


Data courtesy of Hoffmann-La Roche, Inc.
Japan : IMS Quarterly Rx Data until June 2007, Biannual data until June 2007
United States : IMS Weekly prescriptions until June 2007
Rest of World : IMS MIDAS Quarterly Retail data (Germany, France, Brazil, Canada) until June 2007
Season refers to Oct-June data only
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Tamiflu® (oseltamivir) Safety Update:

Pediatric Death Reports (U.S. approval to 05/31/07)

Oseltamivir – Pediatric Deaths

- Total of **25 pediatric deaths** in AERS database through May 31, 2007
- 17 males, 8 females
- Source: Japan-21, US-3, Egypt-1
- 7 new reports since Nov 2006 update including 2 reports due to traumatic injuries from falls in Feb. '07



Oseltamivir - Pediatric Deaths cont.

- 25 Pediatric Deaths through May 31, 2007
 - 5 from traumatic injuries (all from Japan)
 - 9 reports of sudden death (all from Japan)
 - 2 complications of influenza (both from US)
 - 2 cardio-pulmonary arrest (both from Japan)
 - 1 each: Avian influenza (Egypt), acute pancreatitis, pneumonia, asphyxiation, possible encephalitis/cardiomyopathy, sepsis, unspecified death 8-9 months after receiving oseltamivir (US)



Oseltamivir - Pediatric Deaths from Traumatic Injuries (N=5)

5 deaths from traumatic injuries in Japanese ped. pts:

- **17 y/o male, Feb 2004:** after 1 dose of Tamiflu and leapt in front of truck; also received amantadine
- **14 y/o male, Feb 2005:** after 1 dose of Tamiflu fell off the 9th floor
- **12 y/o male Jul 2006:** after 1 dose of Tamiflu found in parking lot presumably due to a fall.
- **14 y/o male, Feb 2007:** after 2 doses of Tamiflu he opened the door and jumped over 1.26 m fence and leapt from the 11th floor.
- **14 y/o female, Feb 2007:** after 1 dose of Tamiflu, mother left patient alone. Within 3 hrs, she apparently fell from the 10th floor.



Oseltamivir Pediatric Deaths: Conclusions

- Based on available data, still difficult to establish a direct causal relationship between the use of oseltamivir and the reported deaths because of:
 - co-morbidity and confounding factors (e.g. influenza) in many of the cases
 - issues with translated reports and limited access to follow-up information make interpreting foreign reports challenging
- However, the contribution of oseltamivir in some of these deaths, especially the fatal reports from traumatic injuries, cannot be completely excluded at this time



Tamiflu® (oseltamivir) Update: Postmarketing (PM) surveillance of Neuropsychiatric Events

Purpose: complete review of all postmarketing reports of neuropsychiatric events with oseltamivir following the 2006-2007 influenza season

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Oseltamivir – Review Methods

- Search of FDA's Adverse Event Reporting System (AERS) database
 - Reports received during time frame:
 - U.S. approval (10/27/99) through 05/31/07
 - MedDRA (Medical Dictionary for Regulatory Activities) terms searched
 - 51 High Level Terms (HLT's)
 - Additional HLT Visual disturbances
 - Suspect Drug = oseltamivir
 - Age = any
- Case categories derived from manual review of reports



Oseltamivir – AERS Results

- 728 AERS reports retrieved
- 132 reports excluded
- 596 cases included in review
 - 444 Japan, 130 US, 22 Other
 - Median age = 14 years (3 months - 94 years)
 - 335 Male, 247 Female, 14 Unknown
 - Time to Onset: median 24 hours (1 or 2 doses)
 - Time to Resolution: median 6 hours
 - 529 treatment, 19 prophylaxis



Oseltamivir - Prophylaxis Cases (N=19)

- **Delirium:** 17 y/o U.S. male was confused after 4 days of oseltamivir. Patient was not sleeping and symptoms progressed to psychosis and paranoia with auditory & visual hallucinations. Patient was hospitalized. Positive urine drug screen (marijuana & benzodiazepines).
- **Suicide attempt:** 49 y/o patient attempted suicide following a night of drinking alcohol. Oseltamivir was initiated one week earlier. Patient also receiving zolpidem.
- **Seizures: 8 patients**
- **Depressed level of consciousness: 2 patients**
- **Loss of consciousness: 2 patients**
- **Miscellaneous: 5 patients**
- **No compelling prophylaxis cases of abnormal behavior**



Neuropsychiatric (NP) Categories

- 1) DIB = Delirium with Impulsive/Injurious Behavior
- 2) DEL = Delirium/Delusions/Hallucinations/Psychosis
- 3) SUI = Suicidal Events
- 4) ANX = Anxiety/Fearful
- 5) PAN = Panic Attack/Disorder
- 6) DLC = Depressed Level of Consciousness
- 7) LOC = Loss of Consciousness/Syncope
- 8) SZ = Convulsions
- 9) MSC = Miscellaneous



Oseltamivir - Cases by NP Category

Category	Ped.	Adult	Unk	Total
DIB (delirium w/injurious behav.)	48	11	---	59
DEL (delirium, hallucination)	176	46	3	225
SUI (suicidal events)	3	9	---	12
SZ (seizures)	50	31	2	83
MSC (miscellaneous)	43	47	20	110
LOC (loss of consciousness)	19	31	---	50
DLC (depressed level of consc.)	17	17	1	35
ANX (anxiety)	2	5	2	9
PAN (panic attacks/disorder)	2	4	1	7
DEL + SZ	5	---	---	5
SZ + DLC	---	1	---	1



Oseltamivir – Pediatric Cases of NP events

Category	0-12 yrs (US)	13-21 yrs (US)	Total (US)
DIB (delirium w/injurious behav.)	23 (2)	25 (1)	48 (3)
DEL (delirium, hallucination)	134 (17)	41 (7)	176* (25)
SUI (suicidal events)	1 (0)	2 (0)	3 (0)
SZ (seizures)	34 (7)	16 (3)	50 (10)
MSC (miscellaneous)	26 (5)	17 (2)	43 (7)
LOC (loss of consciousness)	10 (2)	9 (0)	19 (2)
DLC (depressed level of consc.)	9 (0)	8 (0)	17 (0)
ANX (anxiety)	1 (0)	1 (0)	2 (0)
PAN (panic attacks/disorder)	--	2 (1)	2 (1)
DEL + SZ	4 (0)	1 (0)	5 (0)

* Includes 1 pediatric patient of unspecified age



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Oseltamivir - AERS U.S. reports of delirium with impulsive behavior & self-injury (DIB)

■ **20 month-old male, Feb. 2007;** Patient was afraid of his mother and ran away from her. He was banging his head against the wall to the point where he probably should wear a helmet.

■ **10 y/o male, Feb. 2006;** delirium manifested as throwing lawn chairs off cruise ship and screaming. Ran for the cruise ship railing.

■ **14 y/o male, Feb. 2007;** Patient awoke from sleep delirious & hallucinating, tried to jump out of window. Ranting: "I am going insane, I have to go to doctor."



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Oseltamivir - AERS U.S. report of DIB

14 y/o male, U.S., Feb. 2007: patient received ~2 doses of oseltamivir for influenza. Patient woke up delirious, hallucinating, ran to the window and tried to jump out. He was "acting crazy" and "ranting" and said "I am going insane". The episode lasted about 15 min. Father was advised to take child to ER, but he opted to stay home due to a snowstorm. He was advised to sleep with child in same room and to lock all windows & doors. Child did well overnight. The next morning, a physical exam was unremarkable and neurological exam was normal.



Oseltamivir - AERS reports of DIB from Japan

13 y/o male, Japan, Feb. 2007: Patient took 2 doses of oseltamivir for influenza. Five hours after going to sleep, he felt like he was having a dream where he was chased and then he felt something touch his feet. He found himself hanging from the edge of a 3rd floor window with his feet on a 10 cm ledge. He climbed up and told parents, "I was almost dead. I was terrified". The parents assumed he was dreaming. Next morning, mother noticed the scratches on his forearms and dirty feet. The mother went to his room and saw the open window and footmarks on the ledge. Five hours later, he was afebrile, calm and in good condition at the clinic.



Oseltamivir - AERS reports of DIB from Japan

9 y/o female, Japan, March 2007: Patient took oseltamivir and went to bed. About 30 minutes later, she was heard crying out. When a family member went to see her, she was running to the veranda. The family tried to stop her by force, but she shouted "I must go." The family took her to the bathroom by force, where she shouted and used rude words and threw toilet paper with fixed eyes. She settled down in about five minutes, seemingly regaining consciousness and spoke normally. On visit to the hospital at 4:00pm, she was clear in consciousness.



Oseltamivir - AERS U.S. report of DEL

47 y/o female, U.S., March 2007: I experienced very disturbing side effects with oseltamivir for treatment of flu A. I experienced anxiety and a strange sensation in my head with the 4th dose of oseltamivir. I immediately alerted the prescribing HCP, who suggested trying to get through another day of treatment. After the next dose, I began to hallucinate (swarms of insects). When I closed my eyes I saw sprays of vivid color, and eventually had a very unsettling dream. I struggled to get out of bed to notify a family member and to keep an eye on me. My condition improved overnight, but I decided to stop oseltamivir. I no longer had a fever, and was caught off-guard with the reaction. There was no warning of this side-effect provided with the drug. I consider this reaction to be very serious because I have four children and my husband was out of town. It was bad enough to be sick with the flu, but to be delusional, was considerably worse and dangerous. I would have appreciated a warning or caution before taking the drug, and possibly a recommendation to discontinue the medication at the first sign of NP symptoms. The results could have been disastrous.



Additional Sources to Search...

- Health Claims Databases
 - MarketScan
 - UnitedHealthCare (UHC) Datasets



Oseltamivir – Results on NP Events from Health Claims Databases

Noteworthy Findings from MarketScan Data

- Pediatric Population – ages 0 -12
 - Hazard Ratios (95% CI)
 - Pneumonia 0.55 (0.42, 0.71)
 - Respiratory 0.69 (0.64, 0.75)
 - Otitis Media 0.74 (0.66, 0.83)

Noteworthy Findings from Second Analyses of UHC Data

- UnitedHealthCare (reported by Roche):
 - OR (95% CI)
 - Encephalitis (0-16 years): 0.41 (0.17, 0.99)
- UnitedHealthCare (reported by Ingenix):
 - OR (95% CI)
 - Affective Psychosis (0-17 years): 1.69 (1.13, 2.53)



Oseltamivir – Comments on NP Events from Health Claims Databases

Strengths

- Large robust datasets were used
- The second round of analyses stratified results by appropriate age groups.
- Information provided on how psychiatric outcomes were defined.
- Reported on events that occurred within 14 days of influenza diagnosis.

Challenges

- *Neuropsychiatric events may not be fully captured using health claims data.*
- Small number of events make it difficult to achieve statistical significance
- Uncertain validity of neuropsychiatric event diagnoses
- Lack of information on possible unmeasured confounders



Oseltamivir – NP Event Summary

■ Conclusions

- Continue to receive reports of abnormal behavior.
- Still no compelling cases of abnormal behavior with prophylaxis
- Since last update, there are U.S. reports of abnormal behavior, including impulsive, injurious behavior.
- Events have abrupt onset & rapid resolution
- Events occurred even with adult supervision
- Still difficult to definitively determine if events are due to drug, disease or both.



Review of Neuropsychiatric Events with Other Antivirals for Influenza:

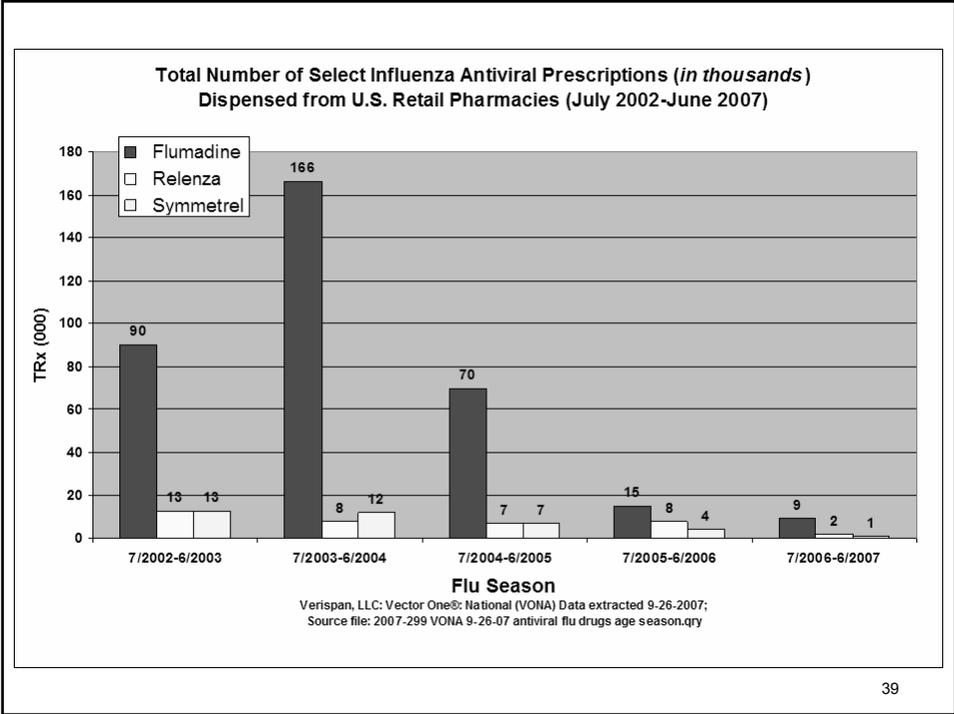
- **Relenza™ (zanamivir)**
- **Symmetrel® (amantadine HCl)**
- **Flumadine® (rimantadine HCl)**

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Drug Use:

- **Relenza™ (zanamivir)**
- **Symmetrel® (amantadine HCl)**
- **Flumadine® (rimantadine HCl)**

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Relenza™ (zanamivir)

Neuropsychiatric Adverse Events

Zanamivir - Background

- **Drug:** Relenza™ (zanamivir) oral inhalation powder
- **Therapeutic Class:** Neuraminidase inhibitor
- **Sponsor:** GlaxoSmithKline
- **Indications:**
 - Treatment of influenza (\geq 7 yrs)
 - Prophylaxis of influenza (\geq 5 yrs)
- **Labeled CNS Reactions:** seizures, syncope



Zanamivir – Review Methods

- Search of FDA's AERS database
 - Reports received during time frame:
U.S. approval (7/26/99) through 08/01/07
 - MedDRA terms searched
 - 51 HLTs
 - Suspect or Concomitant Drug = zanamivir
 - Age = any
- Case categories derived from manual review of reports

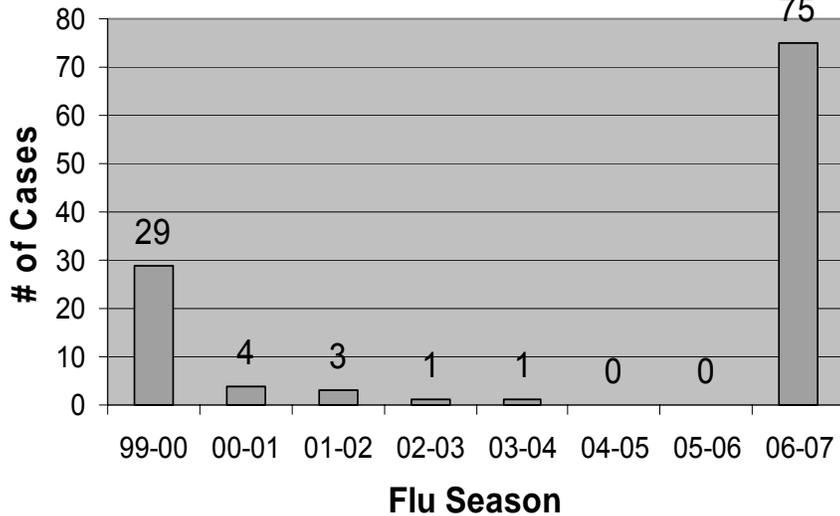


Zanamivir – AERS Results

- 166 AERS reports retrieved
- 51 reports excluded
- 115 cases included in review
 - 81 Japan, 28 US, 6 Other
 - Median age = 13 years (5 - 79 years)
 - 57 Male, 54 Female, 4 Unknown
 - Time to Onset: median 12 hours (1 or 2 doses)
 - Time to Resolution: median 24 hours
 - 109 treatment, 0 prophylaxis



Zanamavir Cases of NP Events per Flu Season, All Ages (N=113)



Zanamivir – Cases by NP Category

Category	Ped.	Adult	Unk	Total
DIB (delirium w/injurious behav.)	6	1	--	7
DEL (delirium, hallucination)	54	5	2	61
SUI (suicidal events)	--	--	--	--
SZ (seizures)	3	8	1	12
MSC (miscellaneous)	6	10	2	18
LOC (loss of consciousness)	2	9	2	13
DLC (depressed level of consc.)	3	--	--	3
ANX (anxiety)	--	1	--	1
PAN (panic attacks/disorder)	--	--	--	--



Zanamivir – Pediatric Cases of NP events

Category	0-12 yrs (US)	13-21 yrs (US)	Total (US)
DIB (delirium w/injurious behav.)	5 (0)	1 (0)	6 (0)
DEL (delirium, hallucination)	41 (1)	13 (0)	54 (1)
SUI (suicidal events)	--	--	--
SZ (seizures)	2 (1)	1 (0)	3 (0)
MSC (miscellaneous)	3 (1)	3 (0)	6 (0)
LOC (loss of consciousness)	--	2 (0)	2 (0)
DLC (depressed level of consc.)	2 (0)	1 (0)	3 (0)
ANX (anxiety)	--	--	--
PAN (panic attacks/disorder)	--	--	--



Zanamivir – AERS reports of DIB

- **5 yr old male (2007 Japan):** 5 hours after 1st dose of zanamivir for influenza abnormal behavior, hallucinations, difficulty speaking and urinary incontinence were noted. Patient said "powdery thing, powdery thing", and uttered other nonsensical phrases. The patient suddenly dashed to the entrance of the house but did not get out. Abnormal behavior occurred again 30 minutes later; patient was mostly absent-minded and came to himself within 10 minutes. Head CT scan - no abnormalities. Patient returned to normal the next day.
- **11 yr-old male, (2007 Japan):** 1 hour after 1st dose of zanamivir for influenza patient suddenly woke up and said, "I can't find the square thing. No, this isn't what I want." He stood up and tried to rush out from the room. "That side is the dream, and this side isn't. I want to go to the dream side." He started to cry out such things as "What's the matter with my life?" He was very much afraid. Patient calmed down in 15 minutes and told mother "I'm okay now."



Zanamivir – NP Event Summary

- **115 cases** of neuropsychiatric events
- **7 cases** of delirium with impulsive, injurious behavior (no fatalities, no U.S. cases)
- **Relationship to influenza suggested by:**
 - Low systemic absorption
 - short latency when fever is likely
 - lack of reoccurrence with subsequent dosing.
- **Relationship to drug suggested by:**
 - short latency
 - recurrence of NP events with multiple dosing
- **Conclusion:** evidence favors influenza-induced etiology, but cannot rule out possible contribution of drug.



Symmetrel® (amantadine HCl)

Neuropsychiatric Adverse Events

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Amantadine - Background

- **Drug:** Symmetrel® (amantadine HCl) oral capsule, tablet & syrup
- **Therapeutic Class:** M2 inhibitor antiviral
- **Sponsor:** Endo Pharmaceuticals
- **Influenza Indications:**
 - Treatment of influenza A (≥ 1 yr)
 - Prophylaxis of influenza A (≥ 1 yr)
- **Labeled CNS Reactions: WARNING - suicide attempts**, seizures, may exacerbate mental problems, disorientation, personality changes, agitation, aggressive behavior, hallucinations, paranoia, other psychotic reactions, insomnia. Also, coma, stupor, delirium, delusions, aggressive behavior, paranoid reaction, manic reaction, EEG changes.



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Amantadine – Review Methods

- Search of FDA’s AERS database
 - Reports received during time frame:
 - U.S. approval through 07/30/07
 - MedDRA terms searched
 - 51 HLTs
 - Primary Suspect Drug = amantadine
 - Age = any
- Case categories derived from manual review of reports
- *Review focused on pediatric cases (subset analysis)*



Amantadine – AERS Results

- **840 AERS reports retrieved**
 - *Review focused on 42 unduplicated pediatric cases*
- **42 cases included in review**
 - 41 US, 1 Canada
 - Median age = 11 years (2.5 – 20 years)
 - 21 Male, 19 Female, 2 Unknown
 - Time to onset: median 5 days
 - 28 treatment, 6 prophylaxis, 8 other/unknown



Amantadine – Cases per NP Category

Category	Pediatric Total
DIB (delirium w/injurious behav.)	---
DEL (delirium, hallucination)	18
SUI (suicidal events)	3
SZ (seizures)	7
MSC (miscellaneous)	4
LOC (loss of consciousness)	---
DLC (depressed level of consc.)	7
ANX (anxiety)	3
PAN (panic attacks/disorder)	---



Amantadine - NP Event Summary

■ Conclusions:

- CNS toxicity is known to occur with amantadine (WARNING in label)
- A subset of neuropsychiatric events (42 pediatric cases) were reviewed
- No additional cases of delirium with impulsive, self-injurious behavior were identified in this subset analysis of pediatric patients



Flumadine[®] (rimantadine HCl)

Safety Update:

Neuropsychiatric Adverse Events

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Rimantadine - Background

- **Drug:** Flumadine (rimantadine HCl) oral capsule and syrup
- **Therapeutic Class:** M2 Inhibitor antiviral
- **Sponsor:** Forest Pharmaceuticals
- **Indications:**
 - Treatment of influenza A in adults
 - Prophylaxis of influenza A in adults & children
- **Labeled CNS Reactions: PRECAUTIONS** – seizures; Controlled clinical trials – impairment of concentration, ataxia, somnolence, agitation, and depression.



Rimantadine – Review Methods

- Search of FDA’s AERS database
 - Reports received during time frame:
U.S. approval (09/17/93) through 05/31/07
 - MedDRA terms searched
 - 51 HLTs
 - Suspect Drug = rimantadine
 - Age = any
- Case categories derived from manual review of reports
- *Review focused on pediatric cases (subset analysis)*



Rimantadine – AERS Results

- **82 AERS reports retrieved**
 - *Review focused on 4 unduplicated pediatric cases*
- **4 cases included in review**
 - Median age = 14.5 years (6-19 years)
 - 4 Male, 0 Female
 - 3 treatment, 1 prophylaxis



Rimantadine – AERS reports of DIB

- 1 pediatric case identified in review
 - 13-year-old male developed hyperactivity, wanted to light matches and became psychotic 4 days after initiating rimantadine for influenza.
- 52 reports of NP events in adult patients reviewed. Similar cases were not found.



Rimantadine – Cases by NP Category

Category	Pediatric Total
DIB (delirium w/injurious behav.)	1
DEL (delirium, hallucination)	1
SUI (suicidal events)	---
SZ (seizures)	1
MSC (miscellaneous)	1
LOC (loss of consciousness)	---
DLC (depressed level of consc.)	---
ANX (anxiety)	---
PAN (panic attacks/disorder)	---



Rimantadine - NP Event Summary

■ Conclusions:

- 4 pediatric cases of neuropsychiatric events reviewed
- One case of delirium with impulsive, self-injurious behavior in a 13-year-old male
- Further review of all adult reports didn't identify any more cases



Summary of Recommendations from DDRE Review:

■ Neuraminidase Inhibitors

- Tamiflu[®] (oseltamivir)
- Relenza[™] (zanamivir)

■ M2 Inhibitors

- Symmetrel[®] (amantadine HCl)
- Flumadine[®] (rimantadine HCl)

Neuraminidase Inhibitors – Recommendations from DDRE Review

- **Tamiflu® (oseltamivir)**
 - Update U.S. label to note that some abnormal, impulsive, injurious behavior cases in Japanese adults & children were fatal, onset was abrupt, and events occurred even while patients were being monitored.
 - No restrictions by age seem warranted at this time in U.S. patients
 - Consider further risk communication (e.g. Public Health Advisory, Prescriber Alert)
 - Unpredictable behavior may lead to injury. Therefore, it may be important to closely supervise children w/ influenza receiving oseltamivir, particularly in the first few days.
 - Continue to monitor post-marketed data.



Neuraminidase Inhibitors – DDRE Recommendations Continued

- **Relenza™ (zanamivir)**
 - Prudent at this time to caution prescribers and patients.
 - Labeling: add **PRECAUTION** describing the PM reports of hallucinations, delirium, and abnormal behavior in patients receiving zanamivir for influenza treatment.
 - Include a statement about monitoring for signs of abnormal behavior throughout the treatment period with zanamivir.
 - Continue to monitor post-marketing data



M2 Inhibitors - Recommendations from DDRE Review

- **Symmetrel® (amantadine HCl)**
- **Flumadine® (rimantadine HCl)**

- No recommendations at this time
- Continue to monitor post-marketing data



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