

Tamiflu Safety Update – 2007

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Outline

- Tamiflu regulatory history
- 2005 BPCA Pediatric Advisory Committee – Recap
- 2006 Update for PAC – Recap
- Summary of new data

Tamiflu Regulatory History

- October, 1999 – Approved for treatment of uncomplicated influenza in adults
- November, 2000 – Approved for prophylaxis of influenza in patients > 13 years (post-exposure and seasonal)
- December, 2000 – Approved for treatment of influenza in pediatric patients > 1 year
- March, 2004 – Pediatric exclusivity granted
- December, 2005 – Approved for post-exposure prophylaxis in patients > 1 year

3

2005 BPCA Review for Pediatric Advisory Committee – Recap

4

BPCA Pediatric Safety Review – Tamiflu – 2005

- OSE reviewed AERS database for pediatric AE cases during the 1-year after granting Tamiflu pediatric exclusivity (3/04-4/05)
- 12 deaths reported in pediatric patients using Tamiflu since approval date
 - All deaths reported from Japan
- 75 pediatric AE cases in database during review period
 - AE reports: 69 Japan, 5 U.S. and 1 Canada
 - Neuropsychiatric events and serious skin reactions were most common

5

Re-analysis of Tamiflu clinical trials data in children – 2005

- In treatment trials one neuropsychiatric serious AE reported
 - 9 year old male with confirmed influenza B, hospitalized with “viral encephalitis”, received placebo
- In prophylaxis trial, 2 adolescents reported with psychiatric events
 - 18 year old male with “psychological disorder” noted present for one month prior to study, received Tamiflu prophylaxis
 - 17 year old female with “nervous breakdown”, history of depression, hospitalized (reported as SAE), received Tamiflu as index case

6

Literature review of influenza-associated encephalitis and encephalopathy in children – 2005

- Increased reports of influenza-associated encephalitis and encephalopathy from Japan beginning in 1990s
- Prompted nationwide surveillance efforts in Japan, medical community and public education of CNS complications of influenza
- Japanese report continued high rates of influenza-related encephalitis and encephalopathy but mortality rates have decreased
- Some suggest decreased mortality due to increased awareness and rapid diagnosis and treatment of influenza among children

7

Additional information requested – 2005

- DAVP/OSE requested additional information from Japanese regulatory authority and Roche regarding neuropsychiatric events
 - Japanese undertook active surveillance of influenza-associated encephalitis and encephalopathy beginning in late 1990s
 - Japanese national health service facilitates rapid diagnostic testing for influenza in children and subsequent treatment
 - Roche/Chugai solicited AE reporting from 70,000 Japanese physicians during 2003-04 flu season

8

FDA conclusions regarding adverse event reports – 2005

- Search of the AERS database for BPCA review (3/04-4/05) identified an unusual pattern of neuropsychiatric AEs, serious skin reactions, and 12 deaths (cumulative) reported with Tamiflu use in pediatric patients
- Re-analysis of the pediatric clinical trials data failed to identify differences in skin and neuropsychiatric AEs between children receiving Tamiflu and placebo/no treatment,

FDA Conclusions Regarding Adverse Event Reports – 2005

- Further investigation into possible reasons for pattern of AEs in Japanese children
 - Syndrome of influenza-associated encephalitis and encephalopathy described in pediatric literature prior to approval of Tamiflu
 - Increased awareness of CNS complications in Japan
 - Increased use of Tamiflu in children in Japan
 - Probable increased levels of AE reporting from Japan during review period

FDA Planned actions – 2005

- DAVP and OSE monthly monitoring of AEs reported with use of Tamiflu and other antivirals during flu season, AE information sharing with CDC
- Any trends could be further investigated
- No plan to change Tamiflu labeling related to deaths or neuropsychiatric AEs
- Update of general pediatric safety information and severe skin reactions planned for label
- Will update PAC on continued AE monitoring at future meeting

11

Committee's requests – 2005

- 2005 PAC agreed with general approach and requested additional data
 - Information from Roche regarding analysis of AEs during Tamiflu prophylaxis compared to treatment
 - Estimate of incidence rates of neuropsychiatric AEs
 - Additional pharmacokinetic, pharmacogenomic, drug metabolism, or effects of CNS inflammation data that might pertain to these AEs
 - Information regarding AEs gleaned from reviews of large health care claims databases
 - Information regarding natural history of influenza, complications of influenza, and management of influenza in pediatric patients in Japan

12

	<h2>2006 Update for Pediatric Advisory Committee – Recap</h2>
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	<h2>2006 Pediatric Advisory Committee Update</h2>
	<ul data-bbox="354 1233 1125 1603" style="list-style-type: none">■ Continued to review AE reports monthly through 2005-2006 flu season■ Update planned after flu season, not full re-evaluation■ OSE developed categories for neuropsychiatric AEs to aid review (descriptive categories) <p data-bbox="1110 1673 1129 1688">14</p>

OSE Review 2006 Summary

- 129 AERS reports identified (all ages) during year since first review (8/29/05 to 7/6/06)
- 26 excluded
 - Narrative did not support
 - Medication errors
 - Confounded by concurrent medical or psychiatric disorders
- 103 cases included in review
 - 95 from Japan, 5 from U.S., 3 from other countries
 - Median age = 12 yrs (range 1½ - 90)
 - Only 3 involved prophylactic use

15

OSE Review 2006 Summary

- Neuropsychiatric AEs (reported between 8/29/05 to 7/6/06, all ages)
 - Delirium with prominent behavioral disturbances – 60 (US-1)
 - Suicidal events – 6 (US-1)
 - Panic attack – 3
 - Delusions – 3
 - Convulsions – 12 (US-1)
 - Depressed level of consciousness – 6
 - Loss of consciousness – 4 (US-1)
 - Miscellaneous – 9 (US-1)

16

OSE Conclusions - 2006

- Characteristics of reports in this follow-up review added uncertainty that events represented a disease-only process
 - Temporality (1 – 2 doses to event)
 - “Drug –effect” as per reporting physician
 - Lack of negative sequelae after de-challenge
 - Absence of frank influenza encephalitis
 - **Peculiar, stereotypical pattern (“abnormal behavior”) of adverse events**
- Concern that if U.S. drug use increases and similar to Japan use, there may be increasing AEs as well

17

FDA Planned Actions - 2006

- DAVP and OSE still uncertain regarding etiology of neuropsychiatric events but believed number and pattern of events warranted precautionary labeling
- Need to closely monitor patient in order to prevent unsafe behavior
- Return next year for full report
 - 2005 PAC suggested that Roche report on studies which address this safety issue.

18

Action taken – 2006

- New wording added to PRECAUTIONS section of Tamiflu label

- Neuropsychiatric Events

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

19

Summary of new data – 2007

20

Where are we now?

- OSE completed full re-evaluation of neuropsychiatric AE reports for all influenza antiviral drugs
 - Refined descriptive categories for use in reviews
- Updated search of pediatric scientific literature (influenza-related events, drug-related events)
- Discussions with Japanese colleagues

21

Where are we now?

- Roche-sponsored studies requested in 2005
 - Attempts to investigate neuropsychiatric events through health claims databases
 - Search safety databases and health claims databases for cases related to prophylaxis
 - Additional scientific evaluation of possible mechanisms

22

Recent clinical reports

- Recent 4-year retrospective review of influenza-related neurologic complications (INC) - 842 pediatric patients with influenza
 - 72 patients identified with INC: encephalopathy (8), post-infectious influenza encephalopathy (2), seizures (56), other (6)
 - Encephalopathy within 3 days of respiratory symptoms, included disorientation, lethargy, visual hallucinations, speech abnormalities
 - Estimated incidence of INC (population-based neighborhood cohort) - 4.1 cases per 100,000 child/years

Newland et al. J Pediatr 2007;150:306.

23

Recent clinical reports

- Follow-up report of similar events from Hong Kong (5 year review) – 874 patients with influenza
 - 182 patients with INC: febrile seizure (165), encephalopathy (5), encephalitis (1)
 - Estimated incidence of INC - 240 per 100,000 person/years
 - “Partly attributable to lower threshold for admission for influenza-related illness and febrile seizure” in Hong Kong population

Chung, et al. J Pediatr 2007;Nov:e17

24

Clinical pharmacology

- Comparison of Tamiflu PK profile in Japanese and Caucasian adults
 - 2 dose levels studied, Days 1 and 7
 - Caucasian subjects taller, heavier, and higher BMI
 - Increased C_{max} among Japanese on Day 1 but not Day 7
 - Authors concluded no clinically significant differences in PK parameters for oseltamivir or oseltamivir carboxylate

Schentag et al. J Clin Pharmacol 2007;47:689

25

New hypotheses regarding etiology of neuropsychiatric AEs

- Nonsynonymous SNP in human cytosolic sialidase increased among Asians – increased binding affinity of sialidase to oseltamivir, reduced sialidase activity, might lead to neuropsychiatric symptoms
- Oseltamivir neuroexcitatory action – pretreatment with Tamiflu increased ethanol-induced sedation in rats and facilitated measures of neuronal excitation in rat hippocampal specimens, suggest that effects of ethanol or other CNS stimulants in combination with Tamiflu may lead to behavioral changes
- Low levels of P-glycoprotein activity in blood-brain barrier may lead to accumulation of oseltamivir in brain and account for neuropsychiatric events

Li C-Y et al. Cell Research 2007;17:357

Izumi Y et al. Neuroscience Letters 2007;426:54

Morimoto K et al. Drug Metab Dispos 2007;Oct 16 online doi:10.1124/dmd.107.017699

26

Summary

- Neuropsychiatric AEs reported with Tamiflu and other influenza drugs
- Increased number of neuropsychiatric AE reports each year since 2005
- Remains difficult to separate symptoms of influenza and drug reactions
- Multiple hypotheses regarding etiology of events and contributing factors – all speculative

27

Questions?

28