

**Set of Questions
for the Adverse Event PAC and Tamiflu Q & As**

General Meeting Questions:

1. Why are certain drugs having their safety reports presented to the Pediatric Advisory Committee on November 18, 2005?

The eight products being reviewed are presently due for a public discussion of their adverse events as required by Section 17 of the Best Pharmaceuticals for Children Act (BPCA). BPCA mandates the review of the adverse event reports received during the one-year after a drug has been granted pediatric exclusivity. The FDA's Office of Pediatric Therapeutics (OPT) is authorized to carry out this mandate and is directed by law to refer such adverse event reports to the Pediatric Advisory Committee (PAC) for their review and recommendations regarding any regulatory actions.

2. What are the drugs being presented on November 18, 2005?

The following drugs, which received their marketing exclusivity at least one year prior to this meeting, will be discussed:

**Anagrelide (Agrylin)
Carboplatin (Paraplatin)
Fluconazole (Diflucan)
Irinotecan (Camptosar)
Oseltamivir (Tamiflu).
Rofecoxib (Vioxx)
Sodium ferric gluconate complex (Ferrlecit)
Sumatriptan (Imitrex)**

3. Why is there an in-depth presentation on Tamiflu (oseltamivir)? What will the presentation include?

The PAC will hear several presentations on oseltamivir (Tamiflu) including adverse event reports, a literature review, and analysis of the clinical trials data. In addition, the sponsor will present data from the clinical trials and safety assessments. A CDC presentation will also provide background information on the United States Surveillance Data on Influenza and their new pediatric influenza surveillance efforts. The review of the adverse event reports for Tamiflu will discuss pediatric deaths, serious skin reactions, and neuropsychiatric events. These events were reported almost entirely in children from Japan.

Specific Questions on Tamiflu:

4. What is Tamiflu and what is it approved for?

Tamiflu (oseltamivir phosphate) is an antiviral drug approved for treatment of uncomplicated influenza A and B in patients 1 year of age or older. It is also approved for prophylaxis (prevention) of influenza in people 13 years or older after household contact or at high risk for exposure during influenza season. Tamiflu is one of a group of anti-influenza drugs called neuraminidase inhibitors that act by blocking the viral enzyme neuraminidase which helps the influenza virus invade cells in the respiratory tract.

5. Does this discussion have anything to do with the pandemic preparations?

The Pediatric Advisory Committee discussion is not directly addressing any issues related to pandemic flu preparations. Indirectly, a better understanding of Tamiflu safety in children will be useful should a pandemic occur and there is widespread use of Tamiflu.

6. Is Tamiflu approved for use in pediatric patients?

Tamiflu is available in both capsule and liquid formulations. It is approved for treatment of influenza in children over 1 year of age. In the U.S., Tamiflu is dosed according to body weight in younger children. Older children (over 40 kg or 88 lbs) and adolescents receive the same dose as adults. It is also approved for prophylaxis (prevention) of influenza in children over 13 years of age.

7. What is useful about Tamiflu in pediatric patients? Who should use it?

When used as directed (twice daily for 5 days) Tamiflu can reduce the duration of influenza symptoms in otherwise healthy children by 1 to 1 ½ days. It also appears to reduce the severity of common flu symptoms. Consequently, it may allow children to return to school or other normal activities sooner. Tamiflu was also shown to be similarly effective in children who had a history of asthma and did not worsen the asthma symptoms.

Tamiflu is most effective when taken within 48 hours after the beginning of flu symptoms and not likely to be effective if patients have already had flu symptoms for several days. Patients (and their parents) should be aware that some patients with influenza may be at risk for secondary bacterial infections and should seek medical care if they are not improving within a few days of beginning Tamiflu.

Tamiflu has not been studied in children with very severe or complicated influenza who require hospitalization and it is not known whether it will provide the same benefit to children with severe illness.

8. What are the important safety issues and adverse events?

When Tamiflu was studied in clinical trials as treatment for children with influenza, children taking Tamiflu experienced similar side effects as children not taking Tamiflu. Serious side effects were not identified. The most common side effects observed in both the treatment and prophylaxis trials were nausea and vomiting. In these trials, a small number of children stopped taking their Tamiflu because of nausea and vomiting or other adverse reactions.

In the safety review mandated by the BPCA, a number of adverse event reports were identified associated with the use of Tamiflu in children 16 years of age or younger. These adverse event reports were primarily related to unusual neurologic or psychiatric events such as delirium, hallucinations, confusion, abnormal behavior, convulsions, and encephalitis. These events were reported almost entirely in children from Japan who received Tamiflu according to Japanese treatment guidelines (very similar but not identical to U.S. treatment guidelines).

The review identified a total of 12 deaths in pediatric patients since Tamiflu's approval. All of the pediatric deaths were reported in Japanese children. In many of these cases, a relationship to Tamiflu was difficult to assess because of the use of other medications, presence of other medical conditions, and/or lack of adequate detail in the reports.

The review also identified severe skin reactions (like allergic reactions) in some pediatric patients. These events were not all reported in Japanese children and have also been reported in adults. Severe skin reactions in all age groups are currently being reviewed in more detail.

9. Why are many of the adverse events being reported from Japan?

Initially, it was not clear why the neuropsychiatric adverse events and deaths were reported almost entirely in Japanese children. The FDA receives adverse event reports from all over the world and usually adverse events are roughly the same from different reporting countries. The reports of death and neuropsychiatric events associated with Tamiflu, almost entirely from Japan, was unusual enough to prompt further evaluation.

The FDA requested additional information from both Hoffman-La Roche, the pharmaceutical company which produces Tamiflu, and the Japanese Ministry of Health, Labor, and Welfare. FDA then evaluated several possible explanations for the neuropsychiatric adverse events.

Was it possible that Japanese patients metabolize Tamiflu differently than American or European patients or have higher levels of the drug in their bodies? There is no scientific evidence that this is true and Japanese dosing recommendations are very similar to U.S. and European recommendations.

Was it possible that these events were an unusual manifestation of influenza infection? There is good evidence that neuropsychiatric events can occur with influenza, in the absence of Tamiflu or other treatment. Beginning in the mid-1990s, there have been many reports in the pediatric scientific literature describing a syndrome of influenza-associated encephalitis (inflammation of the brain) or encephalopathy. These reports originated primarily from Japan where pediatricians described a pattern of rapid onset of fever, accompanied by convulsions and altered level of consciousness, progressing to coma within a few days of the onset of flu symptoms. This syndrome frequently resulted in death or significant neurologic sequelae. These reports prompted nationwide surveillance of influenza-associated encephalopathy in Japan. This syndrome was described and the surveillance in Japan was in progress before Tamiflu was approved for the treatment of influenza.

Was it possible that the large number of adverse events from Japan was because the Japanese use more Tamiflu? Is it possible that we may see more U.S. cases as use of Tamiflu increases in this country? Partly because of the awareness in Japan of influenza-associated encephalopathy, the Japanese health service will pay for rapid diagnostic testing for influenza in children and subsequent treatment. Japan currently uses the majority of the world's supply of Tamiflu distributed for seasonal influenza. It is possible that some of these events might be observed in the U.S. population if the use of Tamiflu increases substantially.

Finally, was it possible that the neuropsychiatric events reported from Japan reflect different methods and requirements for adverse event reporting? Both the Japanese Ministry of Health, Labor and Welfare and Roche confirmed that Japanese regulators require an intensive period of active adverse event reporting for 6 months after a product is approved. When Tamiflu was approved for prophylaxis of influenza in Japan, Roche and its Japanese pharmaceutical affiliate actively solicited adverse event reports from 70,000 institutions and physicians in Japan. These adverse event reports included the 2003-04 flu season and were subsequently reported to the FDA and are included in the BPCA safety review.

It is particularly difficult to assess the relationship of Tamiflu to the reported pediatric deaths. It is known that young children (less than 2 years of age) are hospitalized more often for influenza-associated illness than older children and young adults. Infants and the elderly are known to have higher influenza-associated death rates than other age groups. However, in the U.S., influenza

deaths in children were not among the events requiring reporting to public health departments and the CDC until the 2004-05 flu season.

Review of the available information on the safety of Tamiflu in pediatric patients suggests that the increased reports of neuropsychiatric events in Japanese children are most likely related to an increased awareness of influenza-associated encephalopathy, increased access to Tamiflu in that population, and a coincident period of intensive monitoring adverse events. Based on the information available to us, we can not conclude that there is a causal relationship between Tamiflu and the reported pediatric deaths.

10. What are FDA's next steps?

The evaluation of the pediatric adverse events will be discussed in more detail at the Pediatric Advisory Committee on November 18, 2005; FDA looks forward to comments from the Advisory Committee members. FDA anticipates it will continue to monitor the adverse event profile, including neuropsychiatric adverse events, in all ages including pediatric patients, and will report back to the Pediatric Advisory Committee within 2 years. Through these activities we expect to further refine our understanding of the adverse event profile of Tamiflu. As we did last flu season, we will continue to collaborate with the Centers for Disease Control and Prevention to share information regarding influenza surveillance in the U.S. population and the use of antivirals, including Tamiflu, for treatment.

11. What should I do about this information?

If you or your child is receiving Tamiflu for the treatment of influenza and you are concerned that you may be experiencing a drug-related adverse event, you should contact your physician for advice and management. Adverse events should be reported to the FDA through the on-line MedWatch system or by phone.

Keep in mind that the most effective way to prevent influenza and its complications is by getting the annual influenza vaccine. Children younger than or equal to 8 years of age receiving their first influenza vaccine should receive the vaccine split into 2 doses given one month apart. Children from 6 months to 2 years of age and those with certain underlying medical conditions are considered at high risk for developing complications of influenza and are strongly encouraged to get the vaccine.