Tamiflu Deemed Safe for Children Despite Reports

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GAITHERSBURG, MD. — Tamiflu appears to have played "no role" in the deaths of 12 children in Japan and in 32 reported cases of neuropsychiatric events, 31 of which also occurred in Japan, in children who received the drug after a diagnosis of influenza, the Food and Drug Administration's Pediatric Advisory Committee told the FDA and a swarm of reporters.

The panel recommended, however, that new information be added to the Tamiflu label about the possibility of serious skin reactions.

And it requested that the FDA present the committee with a "preliminary report" of findings from continued monitoring of adverse events as soon as more data are available, "even if it's only after one more flu season."

Tamiflu, or oseltamivir, was one of eight drugs reviewed as part of a mandated 1-year postpediatric exclusivity review of adverse events.

The Best Pharmaceuticals for Children Act requires the FDA's Office of Pediatric Therapeutics to review adverse events reports received during the year after a drug is granted pediatric exclusivity, and to then refer these reports to the Pediatrics Advisory Committee for its review and recommendations.

The report on Tamiflu took on added significance because FDA officials had—independent of the exclusivity review—identified and begun investigating Japanese case reports of death and neuropsychiatric events as a result of a new monitoring system that was put in place during last year's influenza season.

News of pandemic flu preparations and reports that Tamiflu is being made available for pandemic stockpiling also fueled

FDA Panel Clears Two Other Drugs

Sumatriptan and fluconazole were among the drugs that received a green light for routine adverse event monitoring by the Food and Drug Administration's Pediatric Advisory Committee.

The committee gave the thumbs-up after the FDA reported that there were no new unlabeled safety concerns identified in the pediatric adverse events that were reported during the drugs' 1-year postexclusivity periods.

There were six unduplicated pediatric adverse events reports associated with the sumatriptan (Imitrex) nasal spray for treatment of migraine, and none of the reports were serious or life threatening, reported Susan McCune, M.D., a medical officer in the FDA's division of pediatric drug development, Rockville, Md.

For the antifungal fluconazole (Diflucan), there were 19 unduplicated reports of adverse events in children, including four deaths. Most reports were "highly confounded" by underlying illness and concomitant medications, and "although serious adverse events occurred, most were expected or addressed in the drug's labeling," said Larry Grylack, M.D., also of the FDA's division of pediatric drug development.

The 15 nonfatal adverse events reported in patients taking Diflucan involved the following: congenital anomalies in three reports, cardiac events in three, metabolic problems in two, hepatic problems in two, nonfatal fungemia in two, dosing errors in two, and hypersensitivity in one.

Dr. Grylack also reported that there were no new safety concerns identified for the NSAID rofecoxib (Vioxx). During a 7-month exclusivity period, there were 19 pediatric reports, including three foreign deaths, associated with the drug. No further monitoring is necessary, he said, since the drug has been withdrawn from the market.

The other drugs reviewed that also had no new safety concerns were antineoplastic agent irinotecan (Camptosar), antineoplastic agent carboplatin (Paraplatin), platelet-reducing agent anagrelide (Agrylin), and hematinic agent sodium ferric gluconate complex (Ferrlecit).

the interest. The FDA, in material made public before the committee meeting, said that "a better understanding of Tamiflu safety in children will be useful should a pandemic occur."

Tamiflu was first approved in 1999 for the treatment of influenza in adults. Approval of the Tamiflu oral suspension for treatment in children aged 1 year and up followed in 2000, as did approval for prophylaxis for adults and children aged 13 and up. An application for approval for prophylaxis in children aged 1-12 years is pending.

During the period of time covered by its postexclusivity review—from March 2004 to April 2005—there were 75 adverse event reports concerning children up to 16 years of age. The majority—69 of the reports—were from Japan, 5 were from the United States, and 1 was from Canada.

Eight of the reports, all from Japan, were of deaths. Of the 67 nonfatal reports, 32 were classified as CNS reports such as hallucinations, convulsions, delirium, and abnormal behavior; 12 were deemed skin/hypersensitivity reports, and 23 covered gastrointestinal and other events.

Since the time of approval, there have been 190 reports of serious adverse events in children up to age 16 years (28 of them in the United States), and 12 of them deaths in Japan.

Some of the reported deaths involved children who died suddenly within 1-2 days of starting treatment; other deaths occurred later. Some of the children were reported to be previously healthy, and others had asthma or other medical problems. Brain and pulmonary edema were reported in some cases, encephalopathy in others. One report says that a 14-year-old boy "took his own life" after taking Tamiflu, said Melissa Truffa, a registered pharmacist with the FDA's division of drug risk evaluation in Rockville, Md.

In general, many of the cases involve comorbidities and confounding factors, and the majority have limited or missing data. Combined with the fact that neurologic complications are not uncommon during influenza viral infections, "it's difficult to establish a direct casual relationship between the use of oseltamivir and the reported deaths," Ms. Truffa told the committee.

Influenza-associated encephalopathy and neuropsychiatric events have been a concern in Japan for over a decade, and national surveillance is strong. The Japanese national health service also facilitates rapid diagnosis and early treatment of influenza, said Linda Lewis, M.D., of the FDA's division of antiviral products in Rockville.

This, said panel member Janet Englund, M.D., stands in stark contrast to the United States. "We are not good at diagnosing influenza. … We absolutely underdiagnose it," said Dr. Englund, of Children's Hospital and Regional Medical Center in Seattle. "And I know that in our region, there have been shortages [of Tamiflu]. … It's just not used that much."

According to the drug's manufacturer, Hoffman-La Roche, since 2001 there have been 24.5 million prescriptions in Japan, 11.6 million of them for children. In the United States, there have been 6.5 million prescriptions—approximately 872,000 of them for children.

According to Ms. Truffa, while the overall number of Tamiflu prescriptions has risen in the United States in the past 2 years, the percentage of total prescriptions that are written for children has declined from 40% 3 years ago to 25% last year.

The reports of death and neuropsychiatric adverse events from Japan most likely reflect greater use of the drug and more reporting of influenza-associated adverse events; they may partly reflect unknown pathophysiologic differences, Dr. Lewis said. Dosing, she noted, is similar in the United States and Japan.

It is possible, she said, "that similar events might be reported in the United States if Tamiflu use increases substantially or, especially, if awareness of neuropsychiatric complications [of influenza] increases."

Of the 12 reports of skin hypersensitivity reactions that were filed during Tamiflu's postexclusivity period, four cases were "notable cases" that "could have possibly been caused by Tamiflu," Ms. Truffa told the committee.

These and other cases identified from a review of adverse events from the 2004-2005 flu season prompted the FDA to further investigate all reports of serious skin and hypersensitivity reactions. Officials found 16 reports of serious skin reactions, 18 reports of anaphylaxis, and 1 associated death in children from the time of Tamiflu's approval to April 2005.

Additional data are currently under review, and the FDA will propose additional information in the Tamiflu labeling regarding serious skin reactions, FDA officials told the committee.

Current labeling lists dermatitis, rash, swelling of the face or tongue, and toxic epidermal necrolysis as observed and adverse reactions of the drug.

A reanalysis of data from the pediatric clinical trials of Tamiflu, as well as a literature review, failed to identify any differences in both skin and neuropsychiatric adverse events between children with influenza who received Tamiflu and those who received placebo or no treatment, Dr. Lewis said. ■