



December 2003

Dear Health Care Professional:

Roche Laboratories Inc. is writing to inform you of new preclinical safety data that have implications for the use of Tamiflu® (oseltamivir phosphate) in very young children. Tamiflu is indicated for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days. Tamiflu is also indicated for the prophylaxis of influenza in adult patients and adolescents 13 years and older. **Tamiflu is not indicated for either treatment or prophylaxis of influenza in patients less than 1 year of age.**

The early start of the 2003-04 influenza season, together with early reports of increased hospitalizations and deaths in children, has raised concern among parents and physicians about influenza this year. CDC estimates that the serious complications of influenza, including pneumonia, hospitalize about 114,000 people annually in the United States in an unremarkable season. Some health experts estimate that the death toll from this year's outbreak will exceed the annual average of 36,000 people. Of particular concern is that at least 42 children under age 18 have died so far this season from illness attributed to influenza and its complications.

While Tamiflu has been demonstrated to be effective and well tolerated in treating patients as young as 1-year-old, preclinical findings in juvenile rats have raised possible concerns regarding the use of Tamiflu in infants less than 1 year of age. A single dose of 1000 mg/kg oseltamivir phosphate (about 250 times the recommended dose in children) in 7-day-old rats resulted in deaths associated with unusually high exposure to both oseltamivir and oseltamivir phosphate. Further studies showed levels of oseltamivir phosphate in the brain to be approximately 1500 times those seen in adult animals. It is likely that these high exposures are related to an immature blood-brain barrier. Studies showed no deaths or other significant effects in older juvenile rats given the same or higher doses of Tamiflu. The exposures to oseltamivir phosphate associated with no adverse effects in the brain of juvenile rats correspond to approximately 800-fold the exposure expected in a 1-year-old child. The clinical significance of these preclinical data to human infants is uncertain. However, given the uncertainty in predicting the exposures in infants with immature blood-brain barriers, it is recommended that Tamiflu not be administered to children younger than 1 year, the age at which the human blood-brain barrier is generally recognized to be fully developed.

Details of these preclinical findings have been discussed with the Food and Drug Administration, and we are in the process of incorporating the information into the Tamiflu package insert. Given the possible desire to treat very young children with Tamiflu during this active influenza season, **we wish at this time to emphasize the importance of using Tamiflu only for labeled indications and only in patients 1 year and older.**

These data do not affect the use of Tamiflu in older children or in adults. In clinical trials, patients 1 year and older who were treated with Tamiflu within 2 days of symptom onset experienced a reduction in the duration of flu of about 1.5 days. Tamiflu is also effective in preventing the spread of influenza in close contacts in adolescents aged 13 years and older and in adults. The enclosed complete product information includes details on dosing and duration of treatment and prophylaxis for patients within labeled indications.

We would also like to remind you about FluSTAR™, a state-of-the-art surveillance network for tracking and reporting flu. Information about FluSTAR™ can be accessed by visiting www.flustar.com.

If you have any questions or require additional information concerning Tamiflu, please contact the Roche Pharmaceuticals Service Center at 1-800-526-6367.

Roche Laboratories is committed to providing you with the most current product information for Tamiflu. You can assist us in monitoring the safety of Tamiflu by reporting adverse reactions to Roche Laboratories at 1-800-526-6367, by FAX at 1-800-532-3931, via www.fda.gov/medwatch, or by mail to MedWatch, HF-2, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Sincerely,

Dominick Iacuzio, PhD

Medical Director, Roche Laboratories Inc.

Enclosure: Complete Product Information for Tamiflu® (oseltamivir phosphate) Capsules and for Oral Suspension