Roche

September 23, 2009

IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

Roche Laboratories Inc. would like to bring to your attention information on dosing with TAMIFLU® for Oral Suspension contained in the TAMIFLU® (oseltamivir phosphate) package insert.

Consistent with CDC recommendations on September 22, 2009 to the "Updated Interim Recommendations for the Use of Antiviral Medications in the Treatment and Prevention of Influenza for the 2009-2010 Season," health care providers and pharmacists should be aware that the oral dosing dispenser provided with TAMIFLU® for Oral Suspension is marked with 30 mg, 45 mg, and 60 mg graduations, rather than graduations in milliliters (mL) or teaspoons (tsp). Dose recommendations in the dosing tables in the TAMIFLU package insert are provided in milligrams (mg), and associated dosing volumes are footnoted below.

There have been cases where the units of measure in the instructions on the prescription label (mL, tsp) did not match the units on the dosing device (mg), which has in turn led to patient or caregiver confusion and dosing errors. When dispensing commercially manufactured TAMIFLU® for Oral Suspension (12 mg/mL), pharmacists should ensure the units of measure on the prescription instructions match the dosing device:

- If prescription instructions specify administration using milligrams (mg), as per the approved dosing recommendations, then the device included in the Tamiflu® product package should be provided to patients and the prescription label should provide dosing instructions in milligrams (mg).
    - For patients prescribed a 75 mg dose, HCPs should counsel patients that to deliver the full dose, the oral dispenser should first be filled to 45 mg and given to the patient, then refilled to 30 mg to give the remainder of the dose.
- If prescription instructions specify administration using millilters (mL) or teaspoons (tsp), then the device included in the Tamiflu® product package should be removed and replaced with an appropriate measuring device, such as an oral syringe if the prescribed dose is in milliliters (mL).

For ease of use, we have included in Tables 1 and 2 dosing instructions in milligrams and milliliters for both treatment and prophylaxis.

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Table 1 Oral Dose of TAMIFLU for Treatment (twice daily for 5 days) of Influenza in Pediatric Patients One Year of Age and Older by Weight

Body Weight (kg)	Body Weight (lbs)	Recommended Dose for 5 Days	Amount of TAMIFLU for Oral Suspension to Withdraw for Each Dose	Number of Bottles of TAMIFLU for Oral Suspension Needed to Obtain the Recommended Doses for a 5 Day Regimen	Number of TAMIFLU Capsules Needed to Obtain the Recommended Doses for a 5 Day Regimen
≤15 kg	≤33 lbs	30 mg twice daily	2.5 mL	1	10 TAMIFLU Capsules (30 mg)
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg twice daily	3.8 mL	2	10 TAMIFLU Capsules (45 mg)
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg twice daily	5.0 mL	2	20 TAMIFLU Capsules (30 mg)
>40 kg	>88 lbs	75 mg twice daily	6.2 mL	3	10 TAMIFLU Capsules (75 mg)

Table 2 Oral Dose of TAMIFLU for Prophylaxis (once daily for 10 days) of Influenza in Pediatric Patients One Year of Age and Older by Weight

Body Weight (kg)	Body Weight (lbs)	Recommended Dose for 10 Days	Amount of TAMIFLU for Oral Suspension to Withdraw for Each Dose	Number of Bottles of TAMIFLU for Oral Suspension Needed to Obtain the Recommended Doses for a 10 Day Regimen	Number of TAMIFLU Capsules Needed to Obtain the Recommended Doses for a 10 Day Regimen
≤15 kg	≤33 lbs	30 mg once daily	2.5 mL	1	10 TAMIFLU Capsules (30 mg)
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg once daily	3.8 mL	2	10 TAMIFLU Capsules (45 mg)
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg once daily	5.0 mL	2	20 TAMIFLU Capsules (30 mg)
>40 kg	>88 lbs	75 mg once daily	6.2 mL	3	10 TAMIFLU Capsules (75 mg)

We encourage you to become familiar with these dosing instructions. If you have any questions or require additional information concerning TAMIFLU, please contact the Roche Pharmaceuticals Service Center at 1-800-526-6367. In addition, healthcare professionals can access the TAMIFLU complete product information at http://www.rocheusa.com/products/tamiflu/pi.pdf.

In addition, we would like to remind you that should the oral suspension not be readily available, the package insert provides guidance for emergency pharmacy compounding of capsules to produce liquid suspensions (15 mg/mL) for administration to children or adults with difficulty swallowing capsules. **Note: This compounding procedure results in a 15 mg/mL suspension, which is different from the commercially available TAMIFLU for Oral Suspension, which has a concentration of 12 mg/mL.** Similarly, instructions are provided for an extemporaneous preparation of the capsule contents (30, 45, and 75 mg) mixed with sweetened liquids such as regular or sugar-free chocolate syrup for single doses.

For dose adjustments in patients with renal impairment, please refer to the Special Dosage Instructions in the package insert.

Roche Laboratories will continue to monitor the safety of TAMIFLU through established reporting mechanisms and notify regulatory authorities of any serious adverse events for evaluation. We will continue to provide you with the most current product information for TAMIFLU moving forward. You can assist us in monitoring the safety of TAMIFLU by reporting adverse reactions to us at 1-800-526-6367, by FAX at 1-800-532-3931, or to FDA at www.fda.gov/medwatch, or by mail to MedWatch, HF-2, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20851.

Indications

TAMIFLU is indicated for the treatment of uncomplicated influenza caused by viruses types A and B 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 patients 1 year and older.

TAMIFLU is not a substitute for early and annual vaccination as recommended by the Centers for Disease Control's Advisory Committee on Immunization Practices (ACIP).

Influenza viruses change over time. Emergence of resistance mutations could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also diminish clinical benefits of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use TAMIFLU.

Safety Information

Vaccination is considered the first line of defense against influenza.

There is no evidence for efficacy against any illness caused by agents other than influenza types A and B.

Treatment efficacy in subjects with chronic cardiac and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population.

No information is available regarding treatment of influenza in patients at imminent risk of requiring hospitalization.

Efficacy of TAMIFLU has not been established in immunocompromised patients.

Safety and efficacy of repeated treatment or prophylaxis courses have not been studied.

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. TAMIFLU has not been shown to prevent such complications.

The concurrent use of TAMIFLU with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of the potential for interference between these products, LAIV should not be administered within 2 weeks before or 48 hours after administration of TAMIFLU, unless medically indicated.

Influenza can be associated with a variety of neurologic and behavioral symptoms, which can include events such as hallucinations, delirium and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease. There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving TAMIFLU. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made but they appear to be uncommon based on TAMIFLU usage data. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of TAMIFLU to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

In postmarketing experience, rare cases of anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme, have been reported with TAMIFLU.

Adverse events that occurred more frequently in patients treated with TAMIFLU than in patients taking placebo and occurred in ≥2% of patients were (TAMIFLU%, placebo %):

- Treatment in adults – nausea (10%, 6%), vomiting (9%, 3%), bronchitis (2%, 2%)
- Treatment in pediatrics – vomiting (15%, 9%), abdominal pain (5%, 4%), epistaxis (3%, 3%), ear disorder (2%, 1%)
- Prophylaxis of adults – headache (18%, 18%), nausea (7%, 3%), diarrhea (3%, 2%), vomiting (2%, 1%), abdominal pain (2%, 1%)
- Prophylaxis of pediatrics – vomiting (10%, 2%), abdominal pain (3%, 0%), nausea (4%, 1%)

Sincerely,

Hal Barron, MD

Executive Vice President
Head Global Development
Chief Medical Officer