IMPORTANT SUPPLY AND PRESCRIBING INFORMATION

January 14, 2013

RE: Distribution of Tamiflu (Oseltamivir Phosphate) 75 mg capsules from reserve supply with outdated insert labeling

Dear Healthcare Provider:

Due to an early and active influenza season, we are experiencing very high demand for TAMIFLU. To provide additional supply of TAMIFLU, Genentech has released reserve supplies of TAMIFLU 75 mg capsules ("Roche reserve stock"). The medicine from the Roche reserve stock is the same as the medicine that is currently being distributed by Genentech. Importantly, there are some differences in the appearance of the external carton packaging and the enclosed version of the prescribing information. The package configuration is the same as product shipped as recently as two years ago. Please see below for information on the similarities and differences between the two packaging configurations, including revisions to the Emergency Compounding Instructions.

PHARMACISTS: Please remove the outdated package insert from this product before dispensing to patients and distribute the most current patient information, which can be found at Tamiflu.com.

Highlights of the differences between the reserve and current Genentech packaging of TAMIFLU 75 mg capsules:

- *Prescribing Information* – reserve cartons contain an older version from August 2008
    - *Emergency Compounding Instructions* – The most current prescribing information has revised compounding instructions that produce a concentration of 6 mg/mL to match the commercial oral suspension concentration (6 mg/mL) that was introduced in 2011. Please ensure the concentration of the compounded suspension matches the concentration specified on the patient prescription.
    - *New Dosing Information for treatment of pediatric patients 2 weeks to less than 1 year of age*
- *Carton* - reserve stock is branded as Roche, current stock is branded as Genentech

Oral Suspension Supply

Local intermittent shortages of Oral Suspension are expected throughout the remainder of this influenza season due to increased demand. If the commercial manufactured Tamiflu for oral suspension is not readily available, TAMIFLU 75 mg capsules can be compounded into a 6 mg/mL oral suspension. Please refer to the most current version of the prescribing information (dated December 2012) that is enclosed with this letter for updated emergency compounding instructions. The updated prescribing information can also be accessed at http://www.gene.com/download/pdf/tamiflu_prescribing.pdf.

No Impact to Ordering

Genentech does not expect the release of the reserve supplies of TAMIFLU 75 mg capsules to impact your ordering process. The NDC number (NDC 0004-0800-85) and carton dimensions are the same for both configurations. We expect that shipping of these reserve supplies to distributors may begin as early as January 14, 2013. Expiration dating for both configurations is 2016 and you should expect to see both configurations in the marketplace for some time.

Prescribing Information Differences between the Roche reserve stock and Genentech TAMIFLU 75 mg cartons are listed below:

Highlights of the Differences between the 2008 and 2012 versions of the TAMIFLU Prescribing Information for the Oral Suspension and Emergency Compounding		
Date of the Prescribing Information	August 2008	December 2012
Listed Commercial concentration of the Oral Suspension	12 mg/mL (no longer manufactured)	6 mg/mL
Emergency Compounding Instructions*		
- Final Concentration	15 mg/mL	6 mg/mL
- Compounding Vehicles listed	Ora-Sweet SF®, cherry syrup	Ora-Sweet SF®, cherry syrup, and Simple Syrup
- Compounding Directions	Require a mortar and pestle	- Simplified Directions - No mortar and pestle needed
*Emergency compounding directions are not intended to be used if the FDA-approved, commercially manufactured Tamiflu for oral suspension is readily available from wholesalers or the manufacturer.		

The outdated labeling lists the commercially oral suspension concentration as 12 mg/mL and the compounded oral suspension as 15 mg/mL. This outdated labeling and concentrations should not be used.

- **Prescribers:** Please do not prescribe orders with these outdated concentrations.
- **Pharmacists and Nurses:** If these concentrations are prescribed, then immediately contact the physician and request that the prescription is revised to reflect information found in the current insert labeling.

In addition, with the approval of Tamiflu for treatment of acute, uncomplicated influenza in patients 2 weeks of age and older there are revised compounding and dosing instructions. Below is the updated dosing table:

Treatment and Prophylaxis Dosing of TAMIFLU for Influenza in Pediatric Patients[1]

Weight (kg)	Treatment Dosing for 5 days	Prophylaxis Dosing for 10 days[2]	Volume of Oral Suspension (6 mg/mL) for each Dose**	Number of Bottles of Oral Suspension to Dispense	Number of Capsules and Strength to Dispense§
Patients from 2 Weeks to less than 1 Year of Age					
Any weight	3 mg/kg **twice** daily	Not applicable*	0.5 mL/kg†	1 bottle	Not applicable
Patients 1-12 Years of Age Based on Body Weight					
15 kg or less	30 mg **twice** daily	30 mg **once** daily	5 mL	1 bottle	10 Capsules 30 mg
15.1 kg thru 23 kg	45 mg **twice** daily	45 mg **once** daily	7.5 mL	2 bottles	10 Capsules 45 mg
23.1 kg thru 40 kg	60 mg **twice** daily	60 mg **once** daily	10 mL	2 bottles	20 Capsules 30 mg
40.1 kg or more	75 mg **twice** daily	75 mg **once** daily	12.5 mL‡‡	3 bottles	10 Capsules 75 mg

[1] Treatment should begin within 2 days of onset of symptoms, and prophylaxis should begin within 2 days of exposure to an infected individual.

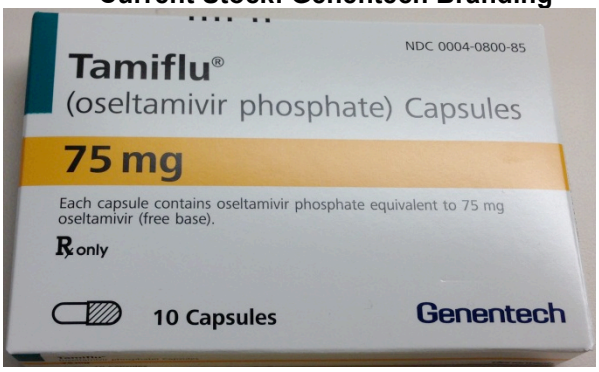
[2] Dose adults and adolescents (13 years and older) following close contact with an infected individual for at least 10 days. Dosing in both adult and pediatric patients (1 to 12 years of age) during a community outbreak is up to 6 weeks in immunocompetent patients.

* TAMIFLU is not approved for prophylaxis of patients less than 1 year of age
**A 10 mL oral dosing dispenser is provided with the oral suspension. In the event that the dispenser provided is lost or damaged, another dosing dispenser may be used to deliver the volumes.
†For patients less than 1 year of age, remove the provided 10 mL oral dosing dispenser from the packaging, and provide an appropriate dosing device that can accurately measure and administer small volumes
‡‡Delivery of this TAMIFLU for Oral Suspension dose requires administering 10 mL followed by another 2.5 mL.
§Oral Suspension is the preferred formulation for patients who cannot swallow capsules.

Packaging Differences between the Roche Reserve Stock and Genentech TAMIFLU 75 mg cartons are listed below:

Reserve Stock : Roche Branding

Current Stock: Genentech Branding



Description	Reserve Stock: Roche Branding TAMIFLU 75 mg Carton	Current Stock: Genentech Branding TAMIFLU 75 mg Carton
Branding	Roche	Genentech
Color Scheme	White carton with black text, red and blue accents	White carton with black text, mustard and teal accents
Capsule Image	White and yellow	Black and white
Distributed by	Roche Laboratories Inc., Nutley, New Jersey 07110	Genentech USA, Inc., A Member of the Roche Group, South San Francisco, CA 94080
Lot/Expiration	Embossed on side of carton	Printed on back of carton

For your reference, below are lot numbers in this product release and their expiry dates:

Lot #	Expiry
U2139	7/31/2016
U2141	7/31/2016
U4116	8/31/2016
U4120-01	9/30/2016
U4122	10/31/2016
U4124	10/31/2016

Please refer to the most current version of the prescribing information (dated December 2012) that can be downloaded at http://www.gene.com/gene/products/information/tamiflu/pdf/pi.pdf.

For more information about TAMIFLU, please visit us at http://www.tamiflu.com/hcp/hcp.jsp.

For medical information questions regarding TAMIFLU, please contact Genentech Medical Communications at 1-800-821-8590 (5:30 a.m.-4 p.m. PST, M-F).

Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail, telephone, or fax.

- **Online**: www.fda.gov/medwatch/report.htm

- **Regular Mail**: use postage-paid, pre-addressed Form FDA 3500 available at: www.fda.gov/MedWatch/getforms.htm. Mail to: MedWatch, 5600 Fishers Lane, Rockville, MD 20857
- **Telephone**: 1-800-332-1088
- **Fax**: 1-800-FDA-0178

Sincerely,

Hal Barron
Genentech USA

Please see Important Safety Information below.

Indications

TAMIFLU is indicated for the treatment of acute, uncomplicated illness due to influenza infection in patients 2 weeks of age 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.

Limitations of Use

- Efficacy of TAMIFLU in patients who begin treatment after 48 hours of symptoms has not been established.
- TAMIFLU is not a substitute for early and annual vaccination as recommended by the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.
- There is no evidence for efficacy of TAMIFLU in any illness caused by agents other than influenza viruses types A and B.
- 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 benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use TAMIFLU.

Important Safety Information

Severe Allergic Reactions

- TAMIFLU is contraindicated in patients who have had severe allergic reactions such as anaphylaxis or serious skin reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme to any component of TAMIFLU.
- In postmarketing experience, cases of anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme, have been reported with TAMIFLU. TAMIFLU should be stopped and appropriate treatment instituted if an allergic-like reaction occurs or is suspected.

Neurologic Symptoms

- 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. Closely monitor patients with influenza for signs of abnormal behavior. If neuropsychiatric symptoms occur, evaluate the risks and benefits of continuing treatment for each patient.

Bacterial Infections

- 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.

Limitations of Populations Studied

- Efficacy of TAMIFLU in the treatment of influenza in patients with chronic cardiac disease 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 with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalization.
- Efficacy of TAMIFLU for treatment or prophylaxis of influenza has not been established in immunocompromised patients.
- Safety and efficacy of TAMIFLU for treatment of influenza in pediatric patients less than 2 weeks of age have not been established.
- Safety and efficacy of TAMIFLU for prophylaxis of influenza have not been established for pediatric patients less than 1 year of age.

Concurrent Use with Live Attenuated Influenza Vaccine

- 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.

Most Common Adverse Reactions

- The safety profile observed in pediatric patients 2 weeks to less than 1 year of age was consistent with the established safety profile of pediatric subjects aged 1 year and older. Vomiting, diarrhea and diaper rash were the most frequently reported adverse reactions in this age group.

- 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%)
    - Treatment in pediatrics—vomiting (15%, 9%), abdominal pain (5%, 4%), ear disorder (2%, 1%)
    - Prophylaxis of adults—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%)

Please see accompanying full Prescribing Information.