CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021246/S-039

Trade Name: **TAMIFLU**

Generic Name: **Oseltamivir Phosphate**

Sponsor: **HOFFMAN-LA ROCHE INC.**

Approval Date: 03/21/2011

Indications:

- 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 indicated for the prophylaxis of influenza in patients 1 year and older.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021246/S-039

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-087/S-056
NDA 21-246/S-039

SUPPLEMENT APPROVAL

Hoffmann-La Roche, Inc.
Attention: Susan Batcha
Program Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Batcha:

Please refer to your Supplemental New Drug Applications (sNDAs) dated September 20, 2010, received September 21, 2010 and October 29, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TAMIFLU (oseltamivir phosphate) Capsules and Oral Suspension.

We acknowledge receipt of your amendments dated November 22, 2010, December 17, 2010, February 11, 2011, February 15, 2011, February 24, 2011 and March 16, 2011.

These Prior Approval supplemental new drug applications provide revisions to the Package Insert, Patient Information and the Carton and Container labeling based on a change in the concentration of the constituted Tamiflu for Oral Suspension from 12 mg/mL to 6 mg/mL, a change to volumetric dosing (from mg to mL), and a change in the Emergency Compounding instructions and final concentration (from 15 mg/mL to 6 mg/mL).

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

At the time the 6 mg/mL oral suspension is introduced to the market, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on March 16, 2011, except with the revisions listed below, as soon as they are available, but no more than 30 days after they are printed.

Revisions to Carton/Container Labeling (These revisions were sent by electronic mail to the applicant on March 18, 2011. The applicant responded by electronic mail on March 21, 2011 and agreed to make the changes listed below):

Carton and container label

1. Please use bold font for: "60 mL (usable volume after constitution)."

Carton label

2. Please use bold font for: "SHAKE WELL BEFORE EACH USE," and "Each mL contains 6 mg oseltamivir base after constitution."

3. On the "Note to pharmacist:" side panel include a usable volume statement of "60 mL (usable volume after constitution)" to appear spaced below the preparation directions.

4. Include the statement "New Strength" on the principal display panel and on at least one other panel. Other panels to consider would include the large panel opposing the principal display panel or the top flap panel. We recommend the color red is utilized to highlight this "New Strength" statement either by printing the statement in red or displaying red as a background color. The statement should be printed on labeling that is anticipated to be introduced into the marketplace during the first 6 months of distribution. The statement may alert or serve as a reminder to pharmacists and pharmacy technicians that a new strength / concentration was introduced into the marketplace.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 21-087/S-056 and NDA 21-246/S-039**." Approval of this submission by FDA is not required before the labeling is used.

MARKET PACKAGE

Please submit one market package of the drug product when it is available.

If sending via USPS, please send to:

Elizabeth Thompson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6234
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS (e.g., UPS, DHL), please send to:

Elizabeth Thompson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6234
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

PROMOTIONAL MATERIALS

We recommend you request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Elizabeth Thompson, M.S., Regulatory Project Manager, at (301) 796-0824.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling (clean)
Carton and Container Labeling (draft clean-*revisions to be sent in officially by applicant)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBRA B BIRNKRANT
03/21/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021246/S-039

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TAMIFLU safely and effectively. See full prescribing information for TAMIFLU.

TAMIFLU® (oseltamivir phosphate) capsules
TAMIFLU® (oseltamivir phosphate) for oral suspension
Initial U.S. Approval: 1999

---------- RECENT MAJOR CHANGES ----------
Dosage and Administration (2.1, 2.2, 2.3, 2.7, 2.8) 3/2011

---------- INDICATIONS AND USAGE ----------
TAMIFLU is an influenza neuraminidase inhibitor indicated for:
- Treatment of influenza in patients 1 year and older who have been symptomatic for no more than 2 days. (1.1)
- Prophylaxis of influenza in patients 1 year and older. (1.2)

Important Limitations of Use:
- Efficacy not established in patients who begin therapy after 48 hours of symptoms. (1.3)
- Not a substitute for annual influenza vaccination. (1.3)
- No evidence of efficacy for illness from agents other than influenza viruses types A and B. (1.3)
- Consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use. (1.3)

---------- DOSAGE AND ADMINISTRATION ----------
Treatment of influenza (2.2)
- Adults and adolescents (13 years and older): 75 mg twice daily for 5 days
- Pediatric patients (1 year and older): Based on weight twice daily for 5 days
- Renally impaired patients (creatinine clearance 10-30 mL/min): Reduce to 75 mg once daily for 5 days (2.4)

Prophylaxis of influenza (2.3)
- Adults and adolescents (13 years and older): 75 mg once daily for at least 10 days
  - Community outbreak: 75 mg once daily for up to 6 weeks
- Pediatric patients (1 year and older): Based on weight once daily for 10 days
  - Community outbreak: Based on weight once daily for up to 6 weeks
- Renally impaired patients (creatinine clearance 10-30 mL/min): Reduce to 75 mg once every other day or 30 mg once daily (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Capsules: 30 mg, 45 mg, 75 mg (3)
- Powder for oral suspension: 360 mg oseltamivir base (constituted to a final concentration of 6 mg/mL) (3)

---------- CONTRAINDICATIONS ----------
Patients with known serious hypersensitivity to oseltamivir or any of the components of TAMIFLU (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Serious skin/hypersensitivity reactions: Discontinue TAMIFLU and initiate appropriate treatment if allergic-like reactions occur or are suspected. (5.1)
- Neuropsychiatric events: Patients with influenza, including those receiving TAMIFLU, particularly pediatric patients, may be at an increased risk of confusion or abnormal behavior early in their illness. Monitor for signs of abnormal behavior. (5.2)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (>1% and more common than with placebo):
- Treatment studies – Nausea, vomiting (6.1)
- Prophylaxis studies – Nausea, vomiting, diarrhea, abdominal pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

---------- DRUG INTERACTIONS ----------
Live attenuated influenza vaccine, intranasal (7):
- Do not administer until 48 hours following cessation of TAMIFLU.
- Do not administer TAMIFLU until 2 weeks following administration of the live attenuated influenza vaccine, unless medically indicated.

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: No data in pregnant women. Use only if clearly needed. (8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing woman. (8.3).
- Pediatric use: Safety and efficacy not established in patients less than 1 year old. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 03/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Influenza

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.

1.2 Prophylaxis of Influenza

TAMIFLU is indicated for the prophylaxis of influenza in patients 1 year and older.

1.3 Limitations of Use

The following points should be considered before initiating treatment or prophylaxis with TAMIFLU:

- Efficacy of TAMIFLU in patients who begin treatment after 48 hours of symptoms has not been established.
- TAMIFLU is not a substitute for early influenza vaccination on an annual basis 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing for Treatment and Prophylaxis of Influenza

TAMIFLU may be taken with or without food *[see Clinical Pharmacology (12.3)]*. However, when taken with food, tolerability may be enhanced in some patients.

The recommended oral treatment and prophylaxis dose of TAMIFLU for patients 1 year of age and older is shown in Table 1.

Table 1 Treatment and Prophylaxis Dosing of Oral TAMIFLU for Influenza For Patients 1 Year of Age and Older Based on Body Weight

Weight (kg)	Weight (lbs)	Treatment Dosing for 5 days	Prophylaxis Dosing for 10 days	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
15 kg or less	33 lbs or less	30 mg **twice** daily	30 mg **once** daily	5 mL	1 bottle	10 Capsules 30 mg
16 kg thru 23 kg	34 lbs thru 51 lbs	45 mg **twice** daily	45 mg **once** daily	7.5 mL	2 bottles	10 Capsules 45 mg
24 kg thru 40 kg	52 lbs thru 88 lbs	60 mg **twice** daily	60 mg **once** daily	10 mL	2 bottles	20 Capsules 30 mg
41 kg or more	89 lbs or more	75 mg **twice** daily	75 mg **once** daily	12.5 mL†	3 bottles	10 Capsules 75 mg

* 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.

†Delivery of this TAMIFLU for Oral Suspension dose requires administering 10 mL followed by another 2.5 mL.

2.2 Standard Dosage – Treatment of Influenza

Adults and Adolescents

The recommended oral dose of TAMIFLU for treatment of influenza in adults and adolescents 13 years and older is 75 mg twice daily for 5 days. Treatment should begin within 2 days of onset of symptoms of influenza. TAMIFLU for oral suspension may be used by patients who cannot swallow a capsule (see Table 1).

Pediatric Patients

TAMIFLU is not indicated for treatment of influenza in pediatric patients younger than 1 year.

The recommended oral dose of TAMIFLU for pediatric patients 1 year and older is shown in Table 1. For pediatric patients who cannot swallow capsules, TAMIFLU for oral suspension is the preferred formulation. If the oral suspension product is not available, TAMIFLU capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup, corn syrup, caramel topping, or light brown sugar (dissolved in water). If the appropriate strengths of TAMIFLU capsules are not available to mix with sweetened liquids and the oral suspension product is not available, then a pharmacist may compound an emergency supply of oral suspension from TAMIFLU 75 mg capsules *[see Dosage and Administration (2.8)]*.

2.3 Standard Dosage – Prophylaxis of Influenza

Adults and Adolescents

The recommended oral dose of TAMIFLU for prophylaxis of influenza in adults and adolescents 13 years and older following close contact with an infected individual is 75 mg once daily for at least 10 days. Therapy should begin within 2 days of exposure. The recommended dose for prophylaxis during a community outbreak of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks in immunocompetent patients. The duration of protection lasts for as long as dosing is continued. Safety has been demonstrated for up to 12 weeks in immunocompromised patients. TAMIFLU for oral suspension may also be used by patients who cannot swallow a capsule (see Table 1).

Pediatric Patients

The safety and efficacy of TAMIFLU for prophylaxis of influenza in pediatric patients younger than 1 year of age have not been established.

The recommended oral dose of TAMIFLU for pediatric patients 1 year and older following close contact with an infected individual is shown in Table 1. For pediatric patients who cannot swallow capsules, TAMIFLU for oral suspension is the preferred formulation. If the oral suspension product is not available, TAMIFLU capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup, corn syrup, caramel topping, or light brown sugar (dissolved in water). If the appropriate strengths of TAMIFLU capsules are not available to mix with sweetened liquids and the oral suspension product is not available, then a pharmacist may compound an emergency supply of oral suspension from TAMIFLU 75 mg capsules *[see Dosage and Administration (2.8)]*.

Prophylaxis in pediatric patients following close contact with an infected individual is recommended for 10 days. Therapy should begin within 2 days of exposure. For prophylaxis in pediatric patients during a community outbreak of influenza, dosing may be continued for up to 6 weeks.

2.4 Renal Impairment

Data are available on plasma concentrations of oseltamivir carboxylate following various dosing schedules in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

Treatment of Influenza

Dose adjustment is recommended for adult patients with creatinine clearance between 10 and 30 mL/min receiving TAMIFLU for the treatment of influenza. In these patients it is recommended that the dose be reduced

to 75 mg of TAMIFLU once daily for 5 days. No recommended dosing regimens are available for patients with end-stage renal disease undergoing routine hemodialysis or continuous peritoneal dialysis treatment.

Prophylaxis of Influenza

For the prophylaxis of influenza, dose adjustment is recommended for adult patients with creatinine clearance between 10 and 30 mL/min receiving TAMIFLU. In these patients it is recommended that the dose be reduced to 75 mg of TAMIFLU every other day or 30 mg TAMIFLU every day. No recommended dosing regimens are available for patients undergoing routine hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

2.5 Hepatic Impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment (Child-Pugh score ≤9) *[see Clinical Pharmacology (12.3)]*.

2.6 Geriatric Patients

No dose adjustment is required for geriatric patients *[see Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)]*.

2.7 Preparation of TAMIFLU for Oral Suspension

It is recommended that TAMIFLU for oral suspension be constituted by the pharmacist prior to dispensing to the patient:

a) Tap the closed bottle several times to loosen the powder.

b) Measure **55 mL** of water in a graduated cylinder.

c) Add the total amount of water for constitution to the bottle and shake the closed bottle well for 15 seconds.

d) Remove the child-resistant cap and push bottle adapter into the neck of the bottle.

e) Close bottle with child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap.

Label the bottle with instructions to Shake Well before each use.

The constituted TAMIFLU for oral suspension (6 mg/mL) should be used within 17 days of preparation when stored under refrigeration or within 10 days if stored at controlled room temperature; the pharmacist should write the date of expiration of the constituted suspension on a pharmacy label. The patient package insert and oral dispenser should be dispensed to the patient.

2.8 Emergency Compounding of an Oral Suspension from 75 mg TAMIFLU Capsules (Final Concentration 6 mg/mL)

The following directions are provided for use only during emergency situations. These 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.

Compounding an oral suspension with this procedure will provide one patient with enough medication for a 5-day course of treatment or a 10-day course of prophylaxis.

Commercially manufactured TAMIFLU for oral suspension (6 mg/mL) is the preferred product for pediatric and adult patients who have difficulty swallowing capsules or where lower doses are needed. In the event that TAMIFLU for oral suspension is not available, the pharmacist may compound a suspension (6 mg/mL) from TAMIFLU capsules 75 mg using one of these vehicles: Cherry Syrup (Humco®), Ora-Sweet® SF (sugar-free) (Paddock Laboratories), or simple syrup. Other vehicles have not been studied. **This compounded suspension**

should not be used for convenience or when the FDA-approved TAMIFLU for oral suspension is commercially available.

First, calculate the total volume of an oral suspension needed to be compounded and dispensed for each patient. The total volume required is determined by the weight of the patient (see Table 2).

Table 2 Volume of an Oral Suspension (6 mg/mL) Needed to be Compounded Based Upon the Patient's Body Weight

Weight (kg)	Weight (lbs)	Total Volume to Compound per Patient (mL)
15 kg or less	33 lbs or less	75 mL
16 thru 23 kg	34 thru 51 lbs	100 mL
24 thru 40 kg	52 thru 88 lbs	125 mL
41 kg or more	89 lbs or more	150 mL

Second, determine the number of capsules and the amount of water and vehicle (Cherry Syrup, Ora-Sweet® SF, or simple syrup) that are needed to prepare the total volume (determined from Table 2: 75 mL, 100 mL, 125 mL, or 150 mL) of compounded oral suspension (6 mg/mL) (see Table 3).

Table 3 Number of TAMIFLU 75 mg Capsules and Amount of Vehicle (Cherry Syrup, Ora-Sweet® SF, or Simple Syrup) Needed to Prepare the Total Volume of a Compounded Oral Suspension (6 mg/mL)

Total Volume of Compounded Oral Suspension to be Prepared	**75 mL**	**100 mL**	**125 mL**	**150 mL**
Number of TAMIFLU 75 mg Capsules*	6 capsules (450 mg oseltamivir)	8 capsules (600 mg oseltamivir)	10 capsules (750 mg oseltamivir)	12 capsules (900 mg oseltamivir)
Amount of Water	5 mL	7 mL	8 mL	10 mL
Volume of Vehicle Cherry Syrup (Humco®) **OR** Ora-Sweet® SF (Paddock Laboratories) **OR** simple syrup	69 mL	91 mL	115 mL	137 mL

*Includes overage to ensure all doses can be delivered

Third, follow the procedure below for compounding the oral suspension (6 mg/mL) from TAMIFLU capsules 75 mg:

1. Place the specified amount of water into a polyethyleneterephthalate (PET) or glass bottle (see Table 3).
2. Carefully separate the capsule body and cap and pour the contents of the required number of TAMIFLU 75 mg capsules into the PET or glass bottle.
3. Gently swirl the suspension to ensure adequate wetting of the TAMIFLU powder for at least 2 minutes.
4. Slowly add the specified amount of vehicle to the bottle.
5. Close the bottle using a child-resistant cap and shake well for 30 seconds to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension. (Note: The

active drug, oseltamivir phosphate, readily dissolves in the specified vehicles. The suspension is caused by inert ingredients of TAMIFLU capsules which are insoluble in these vehicles.)

6. Put an ancillary label on the bottle indicating "Shake Well Before Use."
7. Instruct the parent or caregiver that any unused suspension remaining in the bottle following completion of therapy must be discarded by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date on the label according to storage conditions below.

Storage of the Emergency Compounded Suspension

- Refrigeration: Stable for 5 weeks (35 days) when stored in a refrigerator at 2° to 8°C (36° to 46°F).
- Room Temperature: Stable for five days (5 days) when stored at room temperature, 25°C (77°F).

Note: The storage conditions are based on stability studies of compounded oral suspensions, using the above mentioned vehicles, which were placed in glass and polyethyleneterephthalate (PET) bottles. Stability studies have not been conducted with other vehicles or bottle types.

Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, and drug name and any other required information to be in compliance with all State and Federal Pharmacy Regulations.

Dosing of the Compounded Suspension (6 mg/mL)

Refer to Table 1 for the proper dosing instructions for the pharmacy label.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 30 mg, 45 mg, 75 mg

- 30-mg capsules (30 mg free base equivalent of the phosphate salt): light yellow hard gelatin capsules. "ROCHE" is printed in blue ink on the light yellow body and "30 mg" is printed in blue ink on the light yellow cap.
- 45-mg capsules (45 mg free base equivalent of the phosphate salt): grey hard gelatin capsules. "ROCHE" is printed in blue ink on the grey body and "45 mg" is printed in blue ink on the grey cap.
- 75-mg capsules (75 mg free base equivalent of the phosphate salt): grey/light yellow hard gelatin capsules. "ROCHE" is printed in blue ink on the grey body and "75 mg" is printed in blue ink on the light yellow cap.

For Oral Suspension: 6 mg/mL (final concentration when constituted)

- White powder blend for constitution to a white tutti-frutti–flavored suspension. After constitution, each bottle delivers a usable volume of 60 mL of oral suspension equivalent to 360 mg oseltamivir base (6 mg/mL).

4 CONTRAINDICATIONS

TAMIFLU is contraindicated in patients with known serious hypersensitivity to oseltamivir or any component of the product. Severe allergic reactions have included anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Skin/Hypersensitivity Reactions

Cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme have been reported in postmarketing experience with TAMIFLU. TAMIFLU should be stopped and appropriate treatment instituted if an allergic-like reaction occurs or is suspected.

5.2 Neuropsychiatric Events

Influenza can be associated with a variety of neurologic and behavioral symptoms that 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.

5.3 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.

5.4 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in the labeling:

- Serious skin and hypersensitivity reactions *[see Warnings and Precautions (5.1)]*
- Neuropsychiatric events *[see Warnings and Precautions (5.2)]*

The most common adverse reactions are nausea and vomiting.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment Studies in Adult Subjects

A total of 1171 subjects who participated in adult controlled clinical trials for the treatment of influenza were treated with TAMIFLU. The most frequently reported adverse events in these studies were nausea and vomiting. These events were generally of mild to moderate severity and usually occurred on the first 2 days of administration. Less than 1% of subjects discontinued prematurely from clinical trials due to nausea and vomiting.

Adverse events that occurred with an incidence of ≥1% in 1440 subjects taking placebo or TAMIFLU 75 mg twice daily in adult treatment studies are shown in Table 4. This summary includes 945 healthy young adults and 495 “at risk” subjects (elderly patients and patients with chronic cardiac or respiratory disease). Those events reported numerically more frequently in subjects taking TAMIFLU compared with placebo were nausea, vomiting, bronchitis, insomnia, and vertigo.

Prophylaxis Studies in Adult Subjects

A total of 4187 subjects (adolescents, healthy adults, and elderly) participated in prophylaxis studies, of whom 1790 received the recommended dose of 75 mg once daily for up to 6 weeks. Adverse events were qualitatively very similar to those seen in the treatment studies, despite a longer duration of dosing (see Table 4). Events reported more frequently in subjects receiving TAMIFLU compared to subjects receiving placebo in prophylaxis studies, and more commonly than in treatment studies, were aches and pains, rhinorrhea, dyspepsia and upper respiratory tract infections. However, the difference in incidence between TAMIFLU and placebo for these events was less than 1%. There were no clinically relevant differences in the safety profile of the 942 elderly subjects who received TAMIFLU or placebo, compared with the younger population.

Table 4 Most Frequent Adverse Events in Studies in Naturally Acquired Influenza in Subjects 13 Years of Age and Older

Adverse Event[a]	Treatment				Prophylaxis			
	Placebo N=716		TAMIFLU 75 mg twice daily N=724		Placebo/ No Prophylaxis[b] N=1688		TAMIFLU 75 mg once daily N=1790	
Nausea (without vomiting)	40	(6%)	72	(10%)	56	(3%)	129	(7%)
Vomiting	21	(3%)	68	(9%)	16	(1%)	39	(2%)
Diarrhea	70	(10%)	48	(7%)	40	(2%)	50	(3%)
Bronchitis	15	(2%)	17	(2%)	22	(1%)	15	(1%)
Abdominal pain	16	(2%)	16	(2%)	25	(1%)	37	(2%)
Dizziness	25	(3%)	15	(2%)	21	(1%)	24	(1%)
Headache	14	(2%)	13	(2%)	306	(18%)	326	(18%)
Cough	12	(2%)	9	(1%)	119	(7%)	94	(5%)
Insomnia	6	(1%)	8	(1%)	15	(1%)	22	(1%)
Vertigo	4	(1%)	7	(1%)	4	(<1%)	4	(<1%)
Fatigue	7	(1%)	7	(1%)	163	(10%)	139	(8%)

[a] Adverse events included are all events reported in the treatment studies with frequency ≥1% in the TAMIFLU 75 mg twice daily group.

[b] The majority of subjects received placebo; 254 subjects from a randomized, open-label postexposure prophylaxis study in households did not receive placebo or prophylaxis therapy.

Additional adverse events occurring in <1% of patients receiving TAMIFLU for treatment included unstable angina, anemia, pseudomembranous colitis, humerus fracture, pneumonia, pyrexia, and peritonsillar abscess.

Treatment Studies in Pediatric Subjects

A total of 1032 pediatric subjects aged 1 to 12 years (including 698 otherwise healthy pediatric subjects aged 1 to 12 years and 334 asthmatic pediatric subjects aged 6 to 12 years) participated in controlled clinical trials of TAMIFLU given for the treatment of influenza. A total of 515 pediatric subjects received treatment with TAMIFLU for oral suspension.

Adverse events occurring in ≥1% of pediatric subjects receiving TAMIFLU treatment are listed in Table 5. The most frequently reported adverse event was vomiting. Other events reported more frequently by pediatric subjects treated with TAMIFLU included abdominal pain, epistaxis, ear disorder, and conjunctivitis. These events generally occurred once and resolved despite continued dosing resulting in discontinuation of drug in 8 out of 515 (2%) cases.

The adverse event profile in adolescents is similar to that described for adult subjects and pediatric subjects aged 1 to 12 years.

Prophylaxis Studies in Pediatric Subjects

Pediatric subjects aged 1 to 12 years participated in a postexposure prophylaxis study in households, both as index cases (n=134) and as contacts (n=222). Gastrointestinal events were the most frequent, particularly vomiting. In a separate 6-week, uncontrolled, pediatric seasonal prophylaxis study (n=49), the adverse events noted were consistent with those previously observed (see Table 5).

Table 5 Most Frequent Adverse Events Occurring in Children Aged 1 to 12 Years in Studies in Naturally Acquired Influenza

Adverse Event[a]	Treatment Trials[b]				Household Prophylaxis Trial[c]			
	Placebo N=517		TAMIFLU 2 mg/kg twice daily N=515		No Prophylaxis[d] N=87		Prophylaxis with TAMIFLU once daily[d] N=99	
Vomiting	48	(9%)	77	(15%)	2	(2%)	10	(10%)
Diarrhea	55	(11%)	49	(10%)	-		1	(1%)
Otitis media	58	(11%)	45	(9%)	2	(2%)	2	(2%)
Abdominal pain	20	(4%)	24	(5%)	-		3	(3%)
Asthma (including aggravated)	19	(4%)	18	(3%)	1	(1%)	1	(1%)
Nausea	22	(4%)	17	(3%)	1	(1%)	4	(4%)
Epistaxis	13	(3%)	16	(3%)	-		1	(1%)
Pneumonia	17	(3%)	10	(2%)	2	(2%)	-	
Ear disorder	6	(1%)	9	(2%)	-		-	
Sinusitis	13	(3%)	9	(2%)	-		-	
Bronchitis	11	(2%)	8	(2%)	2	(2%)	-	
Conjunctivitis	2	(<1%)	5	(1%)	-		-	
Dermatitis	10	(2%)	5	(1%)	-		-	
Lymphadenopathy	8	(2%)	5	(1%)	-		-	
Tympanic membrane disorder	6	(1%)	5	(1%)	-		-	

[a] Adverse events included in Table 5 are all events reported in the treatment studies with frequency ≥1% in the TAMIFLU 75 mg twice daily group.
[b] Pooled data from trials of TAMIFLU treatment of naturally acquired influenza.
[c] A randomized, open-label study of household transmission in which household contacts received either prophylaxis or no prophylaxis but treatment if they became ill. Only contacts who received prophylaxis or who remained on no prophylaxis are included in this table.
[d] Unit dose = age-based dosing of 30 mg, 45 mg, or 60 mg

Prophylaxis Study in Immunocompromised Subjects

In a 12-week seasonal prophylaxis study in 475 immunocompromised subjects, including 18 pediatric subjects 1 to 12 years of age, the safety profile in the 238 subjects receiving TAMIFLU was consistent with that previously observed in other TAMIFLU prophylaxis clinical trials.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TAMIFLU. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to TAMIFLU exposure.

Body as a Whole: Swelling of the face or tongue, allergy, anaphylactic/anaphylactoid reactions, hypothermia

Dermatologic: Rash, dermatitis, urticaria, eczema, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme *[see Warnings and Precautions (5.1)]*

Digestive: Hepatitis, liver function tests abnormal

Cardiac: Arrhythmia

Gastrointestinal disorders: Gastrointestinal bleeding, hemorrhagic colitis

Neurologic: Seizure

Metabolic: Aggravation of diabetes

Psychiatric: Abnormal behavior, delirium, including symptoms such as hallucinations, agitation, anxiety, altered level of consciousness, confusion, nightmares, delusions *[see Warnings and Precautions (5.2)]*

7 DRUG INTERACTIONS

Influenza Vaccines

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. The concern about possible interference arises from the potential for antiviral drugs to inhibit replication of live vaccine virus. Trivalent inactivated influenza vaccine can be administered at any time relative to use of TAMIFLU.

Overall Drug Interaction Profile for Oseltamivir

Information derived from pharmacology and pharmacokinetic studies of oseltamivir suggests that clinically significant drug interactions are unlikely.

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases, located predominantly in the liver. Drug interactions involving competition for esterases have not been extensively reported in literature. Low protein binding of oseltamivir and oseltamivir carboxylate suggests that the probability of drug displacement interactions is low.

In vitro studies demonstrate that neither oseltamivir nor oseltamivir carboxylate is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases.

Clinically important drug interactions involving competition for renal tubular secretion are unlikely due to the known safety margin for most of these drugs, the elimination characteristics of oseltamivir carboxylate (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. Coadministration of probenecid results in an approximate two-fold increase in exposure to oseltamivir carboxylate due to a decrease in active anionic tubular secretion in the kidney. However, due to the safety margin of oseltamivir carboxylate, no dose adjustments are required when coadministering with probenecid.

No pharmacokinetic interactions have been observed when coadministering oseltamivir with amoxicillin, acetaminophen, aspirin, cimetidine, antacids (magnesium and aluminum hydroxides and calcium carbonates), or warfarin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are insufficient human data upon which to base an evaluation of risk of TAMIFLU to the pregnant woman or developing fetus. Studies for effects on embryo-fetal development were conducted in rats (50, 250, and 1500 mg/kg/day) and rabbits (50, 150, and 500 mg/kg/day) by the oral route. Relative exposures at these

doses were, respectively, 2, 13, and 100 times human exposure in the rat and 4, 8, and 50 times human exposure in the rabbit. Pharmacokinetic studies indicated that fetal exposure was seen in both species. In the rat study, minimal maternal toxicity was reported in the 1500 mg/kg/day group. In the rabbit study, slight and marked maternal toxicities were observed, respectively, in the 150 and 500 mg/kg/day groups. There was a dose-dependent increase in the incidence rates of a variety of minor skeletal abnormalities and variants in the exposed offspring in these studies. However, the individual incidence rate of each skeletal abnormality or variant remained within the background rates of occurrence in the species studied.

Because animal reproductive studies may not be predictive of human response and there are no adequate and well-controlled studies in pregnant women, TAMIFLU should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

In lactating rats, oseltamivir and oseltamivir carboxylate are excreted in the milk. It is not known whether oseltamivir or oseltamivir carboxylate is excreted in human milk. TAMIFLU should, therefore, be used only if the potential benefit for the lactating mother justifies the potential risk to the breast-fed infant.

8.4 Pediatric Use

The safety and efficacy of TAMIFLU in pediatric patients younger than 1 year of age have not been studied. TAMIFLU is not indicated for either treatment or prophylaxis of influenza in pediatric patients younger than 1 year of age because of the unknown clinical significance of nonclinical animal toxicology data for human infants *[see Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of TAMIFLU for the treatment of influenza, 19% were 65 and over, while 7% were 75 and over. Of the total number of patients in clinical studies of TAMIFLU for the prophylaxis of influenza, 25% were 65 and over, while 18% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

The safety of TAMIFLU in geriatric subjects has been established in clinical studies that enrolled 741 subjects (374 received placebo and 362 received TAMIFLU). Some seasonal variability was noted in the clinical efficacy outcomes *[see Clinical Studies (14.1)]*.

Safety and efficacy have been demonstrated in elderly residents of nursing homes who took TAMIFLU for up to 42 days for the prevention of influenza. Many of these individuals had cardiac and/or respiratory disease, and most had received vaccine that season *[see Clinical Studies (14.2)]*.

8.6 Renal Impairment

Dose adjustment is recommended for patients with a serum creatinine clearance between 10 and 30 mL/min *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*. No recommended dosing regimens are available for patients with end-stage renal disease undergoing routine hemodialysis or continuous peritoneal dialysis treatment.

8.7 Hepatic Impairment

No dosage adjustment is required in patients with mild to moderate hepatic impairment. The safety and pharmacokinetics in patients with severe hepatic impairment have not been evaluated *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

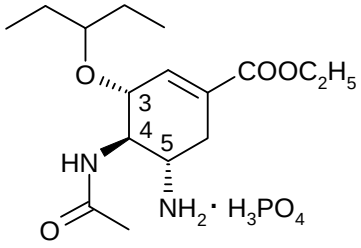
10 OVERDOSAGE

At present, there has been no experience with overdose. Single doses of up to 1000 mg of TAMIFLU have been associated with nausea and/or vomiting.

11 DESCRIPTION

TAMIFLU (oseltamivir phosphate) is available as capsules containing 30 mg, 45 mg, or 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension, which when constituted with water as directed contains 6 mg/mL oseltamivir base. In addition to the active ingredient, each capsule contains pregelatinized starch, talc, povidone K30, croscarmellose sodium, and sodium stearyl fumarate. The 30 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide, and red iron oxide. The 45 mg capsule shell contains gelatin, titanium dioxide, and black iron oxide. The 75 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide. Each capsule is printed with blue ink, which includes FD&C Blue No. 2 as the colorant. In addition to the active ingredient, the powder for oral suspension contains sorbitol, monosodium citrate, xanthan gum, titanium dioxide, tutti-frutti flavoring, sodium benzoate, and saccharin sodium.

Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is $C_{16}H_{28}N_2O_4$ (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt. The structural formula is as follows:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oseltamivir is an antiviral drug *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

Absorption and Bioavailability

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure after oral dosing (see Table 6).

Table 6 Mean (% CV) Pharmacokinetic Parameters of Oseltamivir and Oseltamivir Carboxylate Following Multiple Dosing of 75 mg Capsules Twice Daily (n=20)

Parameter	Oseltamivir	Oseltamivir Carboxylate
C_{max} (ng/mL)	65 (26)	348 (18)
$AUC_{0\text{-}12h}$ (ng·h/mL)	112 (25)	2719 (20)

Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily.

Coadministration with food has no significant effect on the peak plasma concentration (551 ng/mL under fasted conditions and 441 ng/mL under fed conditions) and the area under the plasma concentration time curve (6218 ng·h/mL under fasted conditions and 6069 ng·h/mL under fed conditions) of oseltamivir carboxylate.

Distribution

The volume of distribution (V_{ss}) of oseltamivir carboxylate, following intravenous administration in 24 subjects, ranged between 23 and 26 liters.

The binding of oseltamivir carboxylate to human plasma protein is low (3%). The binding of oseltamivir to human plasma protein is 42%, which is insufficient to cause significant displacement-based drug interactions.

Metabolism

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. Neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome P450 isoforms.

Elimination

Absorbed oseltamivir is primarily (>90%) eliminated by conversion to oseltamivir carboxylate. Plasma concentrations of oseltamivir declined with a half-life of 1 to 3 hours in most subjects after oral administration. Oseltamivir carboxylate is not further metabolized and is eliminated in the urine. Plasma concentrations of oseltamivir carboxylate declined with a half-life of 6 to 10 hours in most subjects after oral administration. Oseltamivir carboxylate is eliminated entirely (>99%) by renal excretion. Renal clearance (18.8 L/h) exceeds glomerular filtration rate (7.5 L/h), indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20% of an oral radiolabeled dose is eliminated in feces.

Special Populations

Renal Impairment

Administration of 100 mg of oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. Oseltamivir carboxylate exposures in patients with normal and impaired renal function administered various dose regimens of oseltamivir are described in Table 7.

Table 7 Oseltamivir Carboxylate Exposures in Patients With Normal and Reduced Serum Creatinine Clearance

Parameter	Normal Renal Function			Impaired Renal Function				
	75 mg once daily	75 mg twice daily	150 mg twice daily	Creatinine Clearance <10 mL/min		Creatinine Clearance >10 and <30 mL/min		
				CAPD	Hemodialysis			
				30 mg weekly	30 mg alternate HD cycle	75 mg daily	75 mg alternate days	30 mg daily
C_{max}	259*	348*	705*	766	850	1638	1175	655
C_{min}	39*	138*	288*	62	48	864	209	346
AUC_{48}†	7476*	10876*	21864*	17381	12429	62636	21999	25054

*Observed values. All other values are predicted.

†AUC normalized to 48 hours.

Hepatic Impairment

In clinical studies oseltamivir carboxylate exposure was not altered in patients with mild or moderate hepatic impairment *[see Dosage and Administration (2.5) and Use in Specific Populations (8.7)]*.

Pediatric Patients

The pharmacokinetics of oseltamivir and oseltamivir carboxylate have been evaluated in a single-dose pharmacokinetic study in pediatric patients aged 5 to 16 years (n=18) and in a small number of pediatric patients aged 3 to 12 years (n=5) enrolled in a clinical trial. Younger pediatric patients cleared both the prodrug and the active metabolite faster than adult patients resulting in a lower exposure for a given mg/kg dose. For oseltamivir carboxylate, apparent total clearance decreases linearly with increasing age (up to 12 years). The pharmacokinetics of oseltamivir in pediatric patients over 12 years of age are similar to those in adult patients.

Geriatric Patients

Exposure to oseltamivir carboxylate at steady-state was 25% to 35% higher in geriatric patients (age range 65 to 78 years) compared to young adults given comparable doses of oseltamivir. Half-lives observed in the geriatric patients were similar to those seen in young adults. Based on drug exposure and tolerability, dose adjustments are not required for geriatric patients for either treatment or prophylaxis *[see Dosage and Administration (2.6)]*.

12.4 Microbiology

Mechanism of Action

Oseltamivir phosphate is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate. Oseltamivir carboxylate is an inhibitor of influenza virus neuraminidase affecting release of viral particles.

Antiviral Activity

The antiviral activity and neuraminidase inhibitory activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture and biochemical assays. The concentrations of oseltamivir carboxylate required for inhibition of influenza virus in cell culture were highly variable depending on the assay method used and the virus tested. The 50% and 90% effective concentrations (EC_{50} and EC_{90}) were in the range of 0.0008 μM to >35 μM and 0.004 μM to >100 μM, respectively (1 μM=0.284 μg/mL). The median IC_{50} values of oseltamivir against influenza A/H1N1, influenza A/H3N2, and influenza B clinical isolates were 2.5 nM (range 0.93-4.16 nM, N=74), 0.96 nM (range 0.13-7.95 nM, N=774), and 60 nM (20-285 nM, N=256), respectively, in a neuraminidase assay with a fluorescently labeled MUNANA substrate. The relationship between the antiviral activity in cell culture, inhibitory activity in the neuraminidase assay, and the inhibition of influenza virus replication in humans has not been established.

Resistance

Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have been recovered by serial passage of virus in cell culture in the presence of increasing concentrations of oseltamivir carboxylate, from clinical isolates collected during treatment with oseltamivir, and from viral isolates sampled during community surveillance studies. Reduced susceptibility of influenza virus to inhibition by oseltamivir carboxylate may be conferred by amino acid substitutions in the viral neuraminidase and/or hemagglutinin proteins. Changes in the viral neuraminidase that have been associated with reduced susceptibility to oseltamivir carboxylate are summarized in Table 8. Hemagglutinin substitutions associated with oseltamivir resistance include A28T and R124M in influenza A H3N2 and H154Q in H1N9, a reassortant human/avian virus.

Table 8 Neuraminidase Amino Acid Substitutions Observed in Oseltamivir Treatment Studies or Community Surveillance

Amino Acid Substitution	Influenza Type/ Sub-type	Source
Catalytic Residues		
R292K	A N2	Roche clinical trials, publication, surveillance[a]
Framework Residues		
H275Y	A N1	Roche clinical trials, publication, surveillance[a]
N294S	A N1, N2	Publications
E119V	A N2	Roche clinical trials, publication, surveillance[a]
SASG245-248 deletion	A N2	Roche clinical trial
I222V	A N2	Publication
I222T	B	Publication
D198N	B	Publication, surveillance[a]
D198E	B	Surveillance[a]
R371K	B	Surveillance[a]
G402S	B	Publication

[a] Substitutions identified by surveillance data only; population and use of TAMIFLU are unknown

Selection of influenza A viruses resistant to oseltamivir can occur at higher frequencies in children. The incidence of oseltamivir treatment-associated resistance in pediatric treatment studies has been detected at rates of 27% to 37% and 3% to 18% (3/11 to 7/19 and 1/34 to 9/50 post-treatment isolates, respectively) for influenza A/H1N1 and influenza A/H3N2, respectively. The frequency of resistance selection to oseltamivir and the prevalence of such resistant virus vary seasonally and geographically.

Circulating seasonal influenza strains expressing neuraminidase resistance-associated substitutions have been observed in individuals who have not received oseltamivir treatment. The oseltamivir resistance-associated substitution H275Y was found in >99% of US circulating 2008 H1N1 influenza isolates. The 2009 H1N1 influenza ("swine flu") was almost uniformly susceptible to oseltamivir. Prescribers should consider available information from the CDC on influenza drug susceptibility patterns and treatment effects when deciding whether to use TAMIFLU.

Cross-resistance

Cross-resistance between oseltamivir and zanamivir has been observed in neuraminidase biochemical assays. The H275Y (N1 numbering) or N294S (N2 numbering) oseltamivir resistance-associated substitutions observed in the N1 neuraminidase subtype, and the E119V or N294S oseltamivir resistance-associated substitutions observed in the N2 subtype (N2 numbering), are associated with reduced susceptibility to oseltamivir but not zanamivir. The Q136K and K150T zanamivir resistance-associated substitutions observed in N1 neuraminidase, or the S250G zanamivir resistance-associated substitutions observed in influenza B, confer reduced susceptibility to zanamivir but not oseltamivir. The R292K oseltamivir resistance-associated substitution observed in N2, and the I222T, D198E/N, R371K, or G402S oseltamivir resistance-associated substitutions observed in influenza B neuraminidase, confer reduced susceptibility to both oseltamivir and zanamivir. In general, amino acid substitutions at neuraminidase catalytic residues confer cross-resistance to other neuraminidase inhibitors while substitutions at framework residues may or may not confer cross-resistance.

No single amino acid substitution has been identified that could confer cross-resistance between the neuraminidase inhibitor class (oseltamivir, zanamivir) and the M2 ion channel inhibitor class (amantadine, rimantadine). However, a virus may carry a neuraminidase inhibitor associated substitution in neuraminidase

and an M2 ion channel inhibitor associated substitution in M2 and may therefore be resistant to both classes of inhibitors. The clinical relevance of phenotypic cross-resistance evaluations has not been established.

Immune Response

No influenza vaccine/oseltamivir interaction study has been conducted. In studies of naturally acquired and experimental influenza, treatment with TAMIFLU did not impair normal humoral antibody response to infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year carcinogenicity studies in mice and rats given daily oral doses of the prodrug oseltamivir phosphate up to 400 mg/kg and 500 mg/kg, respectively, the prodrug and the active form oseltamivir carboxylate induced no statistically significant increases in tumors over controls. The mean maximum daily exposures to the prodrug in mice and rats were approximately 130- and 320-fold, respectively, greater than those in humans at the proposed clinical dose based on AUC comparisons. The respective safety margins of the exposures to the active oseltamivir carboxylate were 15- and 50-fold.

Oseltamivir was found to be non-mutagenic in the Ames test and the human lymphocyte chromosome assay with and without enzymatic activation and negative in the mouse micronucleus test. It was found to be positive in a Syrian Hamster Embryo (SHE) cell transformation test. Oseltamivir carboxylate was non-mutagenic in the Ames test and the L5178Y mouse lymphoma assay with and without enzymatic activation and negative in the SHE cell transformation test.

In a fertility and early embryonic development study in rats, doses of oseltamivir at 50, 250, and 1500 mg/kg/day were administered to females for 2 weeks before mating, during mating and until day 6 of pregnancy. Males were dosed for 4 weeks before mating, during mating, and for 2 weeks after mating. There were no effects on fertility, mating performance or early embryonic development at any dose level. The highest dose was approximately 100 times the human systemic exposure ($AUC_{0\text{-}24h}$) of oseltamivir carboxylate.

13.2 Animal Toxicology and/or Pharmacology

Single, oral administration of ≥657 mg/kg oseltamivir resulted in toxicity, including death, in juvenile 7 day old rats, but had no effect on adult rats. No toxicity was observed after repeated administration of up to 500 mg/kg oseltamivir to developing juvenile rats 7 to 21 days old. This 500 mg/kg dose was approximately 280 and 14 times the human systemic exposure ($AUC_{0\text{-}24h}$) of oseltamivir and oseltamivir carboxylate, respectively. Clinical relevance of the juvenile rat study finding for young infants is unknown.

14 CLINICAL STUDIES

14.1 Treatment of Influenza

Adult Subjects

Two placebo-controlled double-blind clinical trials were conducted: one in the U.S. and one outside the U.S. Subjects were eligible for these trials if they had fever >100ºF, accompanied by at least one respiratory symptom (cough, nasal symptoms, or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue, or headache) and influenza virus was known to be circulating in the community. In addition, all subjects enrolled in the trials were allowed to take fever-reducing medications.

Of 1355 subjects enrolled in these two trials, 849 (63%) subjects were influenza-infected (age range 18 to 65 years; median age 34 years; 52% male; 90% Caucasian; 31% smokers). Of the 849 influenza-infected subjects, 95% were infected with influenza A, 3% with influenza B, and 2% with influenza of unknown type.

TAMIFLU was started within 40 hours of onset of symptoms. Subjects participating in the trials were required to self-assess the influenza-associated symptoms as “none,” “mild,” “moderate,” or “severe.” Time to improvement was calculated from the time of treatment initiation to the time when all symptoms (nasal

congestion, sore throat, cough, aches, fatigue, headaches, and chills/sweats) were assessed as "none" or "mild." In both studies, at the recommended dose of TAMIFLU 75 mg twice daily for 5 days, there was a 1.3 day reduction in the median time to improvement in influenza-infected subjects receiving TAMIFLU compared to subjects receiving placebo. Subgroup analyses of these studies by gender showed no differences in the treatment effect of TAMIFLU in men and women.

In the treatment of influenza, no increased efficacy was demonstrated in subjects receiving treatment of 150 mg TAMIFLU twice daily for 5 days.

Geriatric Subjects

Three double-blind placebo-controlled treatment trials were conducted in subjects ≥65 years of age in three consecutive seasons. The enrollment criteria were similar to that of adult trials with the exception of fever being defined as >97.5°F. Of 741 subjects enrolled, 476 (65%) subjects were influenza-infected. Of the 476 influenza-infected subjects, 95% were infected with influenza type A and 5% with influenza type B.

In the pooled analysis, at the recommended dose of TAMIFLU 75 mg twice daily for 5 days, there was a 1-day reduction in the median time to improvement in influenza-infected subjects receiving TAMIFLU compared to those receiving placebo (p=NS). However, the magnitude of treatment effect varied between studies.

Pediatric Subjects

One double-blind placebo-controlled treatment trial was conducted in pediatric subjects aged 1 to 12 years (median age 5 years), who had fever (>100ºF) plus one respiratory symptom (cough or coryza) when influenza virus was known to be circulating in the community. Of 698 subjects enrolled in this trial, 452 (65%) were influenza-infected (50% male; 68% Caucasian). Of the 452 influenza-infected subjects, 67% were infected with influenza A and 33% with influenza B.

The primary endpoint in this study was the time to freedom from illness, a composite endpoint that required 4 individual conditions to be met. These were: alleviation of cough, alleviation of coryza, resolution of fever, and parental opinion of a return to normal health and activity. TAMIFLU treatment of 2 mg/kg twice daily, started within 48 hours of onset of symptoms, significantly reduced the total composite time to freedom from illness by 1.5 days compared to placebo. Subgroup analyses of this study by gender showed no differences in the treatment effect of TAMIFLU in male and female pediatric subjects.

14.2 Prophylaxis of Influenza

Adult Subjects

The efficacy of TAMIFLU in preventing naturally occurring influenza illness has been demonstrated in three seasonal prophylaxis studies and a postexposure prophylaxis study in households. The primary efficacy parameter for all these studies was the incidence of laboratory-confirmed clinical influenza. Laboratory-confirmed clinical influenza was defined as oral temperature ≥99.0ºF/37.2ºC plus at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one constitutional symptom (aches and pain, fatigue, headache, chills/sweats), all recorded within 24 hours, plus either a positive virus isolation or a four-fold increase in virus antibody titers from baseline.

In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults (aged 13 to 65 years), TAMIFLU 75 mg once daily taken for 42 days during a community outbreak reduced the incidence of laboratory-confirmed clinical influenza from 5% (25/519) for the placebo group to 1% (6/520) for the TAMIFLU group.

In a seasonal prophylaxis study in elderly residents of skilled nursing homes, TAMIFLU 75 mg once daily taken for 42 days reduced the incidence of laboratory-confirmed clinical influenza from 4% (12/272) for the placebo group to <1% (1/276) for the TAMIFLU group. About 80% of this elderly population were vaccinated, 14% of subjects had chronic airway obstructive disorders, and 43% had cardiac disorders.

In a study of postexposure prophylaxis in household contacts (aged ≥13 years) of an index case, TAMIFLU 75 mg once daily administered within 2 days of onset of symptoms in the index case and continued for 7 days reduced the incidence of laboratory-confirmed clinical influenza from 12% (24/200) in the placebo group to 1% (2/205) for the TAMIFLU group. Index cases did not receive TAMIFLU in the study.

Pediatric Subjects

The efficacy of TAMIFLU in preventing naturally occurring influenza illness has been demonstrated in a randomized, open-label, postexposure prophylaxis study in households that included children aged 1 to 12 years, both as index cases and as family contacts. All index cases in this study received treatment. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the household. Laboratory-confirmed clinical influenza was defined as oral temperature ≥100°F/37.8°C plus cough and/or coryza recorded within 48 hours, plus either a positive virus isolation or a four-fold or greater increase in virus antibody titers from baseline or at illness visits. Among household contacts 1 to 12 years of age not already shedding virus at baseline, TAMIFLU for oral suspension 30 mg to 60 mg taken once daily for 10 days reduced the incidence of laboratory-confirmed clinical influenza from 17% (18/106) in the group not receiving prophylaxis to 3% (3/95) in the group receiving prophylaxis.

Immunocompromised Subjects

A double-blind, placebo-controlled study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised subjects (including 18 pediatric subjects 1 to 12 years of age) who had received solid organ (n=388; liver, kidney, liver and kidney) or hematopoietic stem cell transplants (n=87). Median time since transplant for solid organ transplant recipients was 1105 days for the placebo group and 1379 days for the oseltamivir group. Median time since transplant for hematopoietic stem cell transplant recipients was 424 days for the placebo group and 367 days for the oseltamivir group. Approximately 40% of subjects received influenza vaccine prior to entering the study. The primary efficacy endpoint for this study was the incidence of confirmed, clinical influenza, defined as oral temperature >99.0°F/37.2°C plus cough and/or coryza, all recorded within 24 hours, plus either a positive virus culture or a four-fold increase in virus antibody titers from baseline. The incidence of confirmed clinical influenza was 3% (7/238) in the group not receiving TAMIFLU compared with 2% (5/237) in the group receiving TAMIFLU; this difference was not statistically significant. A secondary analysis was performed using the same clinical symptoms and RT-PCR for laboratory confirmation of influenza. Among subjects who were not already shedding virus at baseline, the incidence of RT-PCR-confirmed clinical influenza was 3% (7/231) in the group not receiving TAMIFLU and <1% (1/232) in the group receiving TAMIFLU.

16 HOW SUPPLIED/STORAGE AND HANDLING

TAMIFLU Capsules

30-mg capsules (30 mg free base equivalent of the phosphate salt): light yellow hard gelatin capsules. “ROCHE” is printed in blue ink on the light yellow body and “30 mg” is printed in blue ink on the light yellow cap. Available in blister packages of 10 (NDC 0004-0802-85).

45-mg capsules (45 mg free base equivalent of the phosphate salt): grey hard gelatin capsules. “ROCHE” is printed in blue ink on the grey body and “45 mg” is printed in blue ink on the grey cap. Available in blister packages of 10 (NDC 0004-0801-85).

75-mg capsules (75 mg free base equivalent of the phosphate salt): grey/light yellow hard gelatin capsules. “ROCHE” is printed in blue ink on the grey body and “75 mg” is printed in blue ink on the light yellow cap. Available in blister packages of 10 (NDC 0004-0800-85).

Storage

Store the capsules at 25ºC (77ºF); excursions permitted to 15º to 30ºC (59º to 86ºF) [See USP Controlled Room Temperature].

TAMIFLU for Oral Suspension

Supplied as a white powder blend in a glass bottle. After constitution, the powder blend produces a white tutti-frutti–flavored oral suspension. After constitution with 55 mL of water, each bottle delivers a usable volume of 60 mL of oral suspension equivalent to 360 mg oseltamivir base (6 mg/mL). Each bottle is supplied with a bottle adapter and a 10 mL oral dispenser (NDC 0004-0820-09).

Storage

Store dry powder at 25ºC (77ºF); excursions permitted to 15º to 30ºC (59º to 86ºF) [See USP Controlled Room Temperature].

Store constituted suspension under refrigeration for up to 17 days at 2º to 8ºC (36º to 46ºF). Do not freeze. Alternatively, store constituted suspension for up to 10 days at 25ºC (77ºF); excursions permitted to 15º to 30ºC (59º to 86ºF) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (Patient Information)

17.1 Information for Patients

Patients and/or caregivers should be advised of the risk of severe allergic reactions (including anaphylaxis) or serious skin reactions and should stop TAMIFLU and seek immediate medical attention if an allergic-like reaction occurs or is suspected.

Patients and/or caregivers should be advised of the risk of neuropsychiatric events in patients with influenza and should contact their physician if they experience signs of abnormal behavior while receiving TAMIFLU. Their physician will determine if TAMIFLU treatment should be continued.

Instruct patients to begin treatment with TAMIFLU as soon as possible from the first appearance of flu symptoms. Similarly, prevention should begin as soon as possible after exposure, at the recommendation of a physician.

Instruct patients to take any missed doses as soon as they remember, except if it is near the next scheduled dose (within 2 hours), and then continue to take TAMIFLU at the usual times.

TAMIFLU is not a substitute for a flu vaccination. Patients should continue receiving an annual flu vaccination according to guidelines on immunization practices.

A bottle of TAMIFLU for oral suspension contains approximately 11 g sorbitol. One dose of 75 mg TAMIFLU for oral suspension delivers 2 g sorbitol. For patients with hereditary fructose intolerance, this is above the daily maximum limit of sorbitol and may cause dyspepsia and diarrhea.

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Foster City, California 94404

TUCOS_640796_PI_2011_03(K)

Patient Information

TAMIFLU®

(oseltamivir phosphate)

R_X only

This leaflet contains important information about TAMIFLU (TAM-ih-flew). Read it well before you begin treatment. This information does not take the place of talking with your healthcare professional about your medical condition or your treatment. This leaflet does not list all the benefits and risks of TAMIFLU. If you have any questions about TAMIFLU, ask your healthcare professional. Only your healthcare professional can determine if TAMIFLU is right for you.

What is TAMIFLU?

TAMIFLU attacks the influenza virus and stops it from spreading inside your body. TAMIFLU treats flu at its source, by attacking the virus that causes the flu, rather than simply masking symptoms.

TAMIFLU is for treating adults and children age 1 and older with the flu whose flu symptoms started within the last day or two. TAMIFLU can also reduce the chance of getting the flu in people age 1 and older who have a higher chance of getting the flu because they spend time with someone who has the flu. TAMIFLU can also reduce the chance of getting the flu if there is a flu outbreak in the community.

What is "Flu"?

"The flu" is an infection caused by the influenza virus. Flu symptoms include fever (usually 100ºF to 103ºF in adults, and sometimes higher in children) and problems such as cough, sore throat, runny or stuffy nose, headaches, muscle aches, fever, and extreme tiredness. Many people use the term "flu" to mean any combination of these symptoms, such as the common cold, but true influenza infection is often worse and may last longer than a cold.

Flu outbreaks happen about once a year, usually in the winter, when the influenza virus spreads widely in the community. Outside of those outbreaks, only a very tiny number of respiratory infections are caused by the influenza virus.

Should I get a flu shot?

TAMIFLU is not a substitute for a flu vaccination. You should continue to get a flu vaccination every year, according to your healthcare professional's advice.

Who should not take TAMIFLU?

Do not take TAMIFLU if you are allergic to the main ingredient, oseltamivir phosphate, or to any other ingredients of TAMIFLU. Before starting treatment, make sure your healthcare professional knows if you take any other medicines, or are pregnant, planning to become pregnant, or breastfeeding. TAMIFLU is normally not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown. TAMIFLU is not recommended for use in children younger than 1 year of age.

Tell your healthcare professional if you have any type of kidney disease, heart disease, respiratory disease, or any serious health condition.

TAMIFLU for Oral Suspension contains sorbitol. Sorbitol may cause upset stomach and diarrhea in patients with a family history of fructose intolerance.

How should I take TAMIFLU?

It is important that you begin your treatment with TAMIFLU as soon as possible from the first appearance of your flu symptoms or soon after you are exposed to the flu. If you feel worse or develop new symptoms during treatment with TAMIFLU, or if your flu symptoms do not start to get better, you should contact your healthcare professional.

If you have the flu: Take TAMIFLU twice a day for 5 days, once in the morning and once in the evening. You should complete the entire treatment of 10 doses (capsules or suspension), even if you feel better.

To prevent the flu: If someone in your home has the flu, take TAMIFLU once a day for 10 days or for as long as prescribed. You can take TAMIFLU for up to 6 weeks if you are exposed to the flu because of an outbreak in your community. Follow your healthcare professional's advice on how long to take TAMIFLU.

You can take TAMIFLU with food or without food. There is less chance of stomach upset if you take it with a light snack, milk, or a meal.

If you are taking TAMIFLU for Oral Suspension, your pharmacist will give you a dosing dispenser to measure the proper amount of Oral Suspension for your dose. Follow your healthcare professional's instructions on how to measure the proper dose for you. Review the instructions below on how to use the dispenser and ask your pharmacist if you have any questions. If you lose or damage the dispenser and cannot use it, contact your healthcare professional or pharmacist for advice on the proper dose.

If TAMIFLU for Oral Suspension is not available, your healthcare provider may instruct you to open TAMIFLU Capsules and mix the contents with sweetened liquids such as regular or sugar-free chocolate syrup, corn syrup, caramel topping, or light brown sugar (dissolved in water). Please follow the dosing instructions below.

If you forget to take your medicine, take the missed dose as soon as you remember, except if it is 2 hours or less before your next dose. Then continue to take TAMIFLU at the usual times. Do not take 2 doses at a time to make up for a missed dose. If you miss several doses, tell your healthcare professional and follow the advice given to you.

What are the possible side effects of TAMIFLU?

The most common side effects of TAMIFLU are nausea and vomiting. These are usually mild to moderate. They usually happen in the first 2 days of treatment. Taking TAMIFLU with food may reduce the chance of getting these side effects.

If you develop an allergic reaction or severe rash, stop taking TAMIFLU and contact your healthcare professional.

People with the flu, particularly children and adolescents, may be at an increased risk of seizures, confusion, or abnormal behavior early during their illness. These events may occur shortly after beginning TAMIFLU or may occur when flu is not treated. These events are uncommon but may result in accidental injury to the patient. Therefore, patients should be observed for signs of unusual behavior and a healthcare professional should be contacted immediately if the patient shows any signs of unusual behavior.

Before taking TAMIFLU, please let your healthcare provider know if you have received nasally administered influenza virus vaccine during the past two weeks.

If you notice any side effects not mentioned in this leaflet, or if you have any concerns about the side effects you get, tell your healthcare professional.

How and where should I store TAMIFLU?

TAMIFLU Capsules should be stored at room temperature, 77ºF (25ºC) and kept in a dry place. Keep this medication out of reach of children.

TAMIFLU for Oral Suspension should be stored under refrigeration for up to 17 days at 36º to 46ºF (2º to 8ºC). Do not freeze. Alternatively, store at room temperature for up to 10 days. Discard any unused portion when you are finished with your prescribed dosing of TAMIFLU.

General advice about prescription medicines:

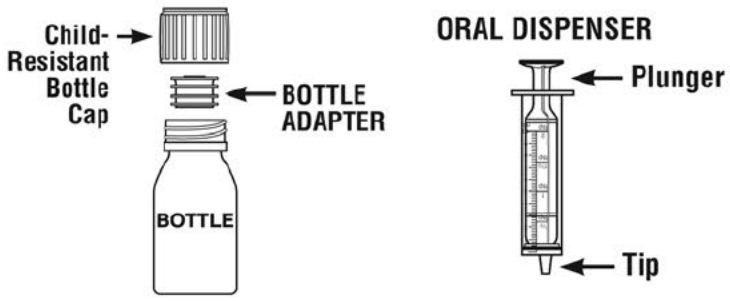
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TAMIFLU for a condition for which it was not prescribed. Do not give TAMIFLU to other people, even if they have the same symptoms you have. It may not be right for them.

This leaflet summarizes the most important information about TAMIFLU. If you would like more information, talk with your healthcare professional. You can ask your pharmacist or healthcare professional for information about TAMIFLU that is written for health professionals.

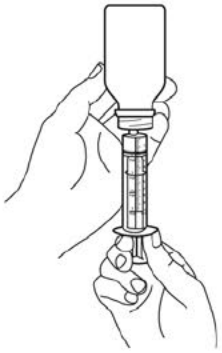
DOSING INSTRUCTIONS FOR PATIENTS:

How Do I Prepare a Dose of TAMIFLU for Oral Suspension?

Please follow instructions carefully to ensure proper dosing of the oral suspension.



- Shake closed bottle well for about 5 seconds before each use.
- Remove child-resistant cap.
- Before inserting the tip of the oral dispenser into bottle adapter, push the plunger completely down toward the tip of the oral dispenser. Insert tip firmly into opening of the bottle adapter.
- Turn the entire unit (bottle and oral dispenser) upside down.
- Pull the plunger out slowly until the desired amount of medication is withdrawn into the oral dispenser (see figure). The 12.5 mL (75 mg) dose is obtained by filling the dispenser twice, once to the 10 mL graduation, and a second fill to the 2.5 mL graduation.



- Turn the entire unit right side up and remove the oral dispenser slowly from the bottle.
- Dispense directly into mouth. Do not mix with any liquid prior to dispensing.
- Close bottle with child-resistant cap after each use.
- Disassemble oral dispenser, rinse under running tap water and air dry prior to next use.

If Directed by My Healthcare Provider, How Do I Mix the Contents of TAMIFLU Capsules with Sweetened Liquids?

Please follow instructions carefully to ensure proper dosing.

- Holding one capsule over a small bowl, carefully pull the capsule open and pour the complete contents of the capsule into the bowl.
- Add to the capsule contents a small amount of a sweetened liquid such as chocolate syrup (regular or sugar-free), corn syrup, caramel topping, or light brown sugar (dissolved in water) that the child will consume completely.
- Stir the mixture and give the entire dose to the child.

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TUCOS_640796_PPI_2011_03(K)

Rev. March 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021246/S-039

MEDICAL REVIEW(S)

Medical Officer's Clinical Review
NDA 21-246, S-039
NDA 21-087, S-056
(Prior Approval Labeling Supplement)

Date Submitted: September 20, 2010
Date Received: September 21, 2010
Date Reviewed: March 16, 2011

Sponsor: Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

Product: Tamiflu® (oseltamivir phosphate) for Oral Suspension, 6 mg/mL

Indication: Treatment and prophylaxis of influenza A and B

Introduction:

This labeling supplement, submitted by Roche, proposes changes to the constitution instructions for Tamiflu for Oral Suspension that will result in a change in final concentration of the suspension to 6 mg/mL. The commercial suspension has previously been constituted by the addition of sterile water to a concentration of 12 mg/mL.

(b) (4)

During the 2009 H1N1 influenza pandemic, increased use of Tamiflu suspension led to identification of multiple issues

(b) (4)

However, the Division of Antiviral Products (DAVP) became aware that the inclusion of the dosing device marked in mg doses was confusing to both prescribers and parents because the convention for dosing pediatric patients in the U.S. is by volume. Additional confusion ensued when supplies of the commercial suspension were exhausted during the pandemic and pharmacists had to rely on the Package Insert (PI) instructions for "Emergency Compounding of an Oral Suspension from Tamiflu Capsules" which resulted in a suspension with a concentration of 15 mg/mL.

In order to decrease the potential for dosing errors, DAVP and Roche discussed multiple possible corrective actions. (b) (4) In order to accomplish this change, Roche has proposed the following changes to the commercial suspension as described in this labeling supplement:

1. The concentration is changing from 12 mg/mL to 6 mg/mL.

2. The product will be dosed by volume (mL rather than mg).

3. The commercial package size (glass bottle) will change from 60-mL to 100-mL.

4. The child-resistant plastic closure is changing from one that required tamper-evident neckbanding to a child-resistant one that has a perforated plastic ring at its base, which breaks apart when the bottle is opened.

5. The (b) (4) oral dispenser will be replaced with a 10-mL dispenser, with no change to the composition or supplier of the dispenser.

6. (b) (4)

7. The text on the bottle label and carton will be revised accordingly, and in addition, the product will be rebranded from Roche to Genentech.

8. The Package Insert will be revised to describe these changes.

In addition, the instructions for emergency compounding suspension from Tamiflu 75 mg capsules have been modified so that the resulting suspension is also 6 mg/mL. This modification involves a change in the amount of vehicle/water added to the capsule contents during compounding.

Brief Review:

Change in concentration of Tamiflu for Oral Suspension

(b) (4)

(b) (4)

The applicant also notes that while some of the shaking/dosing accuracy studies were performed using the smallest pediatric dose (1 mL might be used for dosing a 3 kg infant), Tamiflu is not approved for use pediatric patients < 1 year of age.

Reviewer's comments:
During the 2009 H1N1 influenza pandemic, Roche evaluated dosing accuracy for infants < 1 year of age as part of the Emergency Use Authorization for Tamiflu. As might be expected, (b) (4)

Instructions for pharmacists to prepare a suspension using the contents of Tamiflu 75 mg capsules

In 2006, the DAVP requested Roche provide some mechanism by which pediatric patients for whom the adult size capsules were not appropriate might be dosed with Tamiflu in the event of limited supplies of commercial Tamiflu suspension. This might occur in the setting of an influenza pandemic or a very severe influenza season during which supplies of Tamiflu oral suspension could be exhausted. At that time, only limited supplies of commercial Tamiflu for Oral Suspension were stored in the Strategic National Stockpile (SNS) and Roche had advised the SNS that manufacture of the suspension formulation required more resources than manufacturing Tamiflu Capsules.

The sponsor undertook palatability and stability studies evaluating different vehicles that could be used to mask the bitter taste of oseltamivir phosphate associated with emptied capsule contents. Two products, Cherry Syrup and Ora-Sweet SF, were selected as the best candidates for a pharmacist-compounded formulation based on palatability, availability in the U.S., preservative content, and common usage in pharmaceutical compounding. The compounded formulations were found to be chemically and microbiologically stable for up to 35 days at 5°C and at least 5 days at 25°C/60% RH. Please refer to the Chemistry Review performed by Dr. George Lunn and the Clinical Review performed by this reviewer for details of that NDA S-033. Instructions for pharmacists were incorporated into the Dosage and Administration section of the PI as "Emergency Compounding of an Oral Suspension from Tamiflu Capsules."

For ease of compounding, the instructions for pharmacists provided a suspension containing Tamiflu 15 mg/mL compared to the commercial suspension which contains 12 mg/mL. The difference in concentrations of the commercial suspension and the compounded suspension was emphasized in the PI but during the 2009 H1N1 influenza

pandemic, many reports of confusion regarding the two suspensions were documented. As part of FDA's discussions with the applicant regarding changes in the concentration of commercial suspension, we also requested that the instructions for emergency compounding be revised to provide a suspension with the same concentration as the commercial suspension (6 mg/mL). This supplement provides new instructions for pharmacists for "Emergency Compounding of an Oral Suspension from Tamiflu Capsules" for a single course of treatment or prophylaxis. The new instructions not only provide for the lower concentration but also add another step in the compounding process. Pharmacists are now instructed to open capsules and pour contents into a bottle containing a specified amount of water and swirl to wet the powder. Then a specified volume of vehicle (Cherry Syrup, Ora-Sweet, or simple syrup) is slowly added to the mixture. The bottle is closed and shaken to completely dissolve the active oseltamivir phosphate; some excipients will remain undissolved in the suspension.

Reviewer's comments:
The applicant provided justification and testing for the new steps in the pharmacist compounding instructions and the proposed process appears to be within the scope of many retail pharmacy services. This reviewer believes that aligning the concentrations of both commercial and compounded suspensions will allow clearer dosing instructions for pediatric patients and reduce the potential for dosing errors.

During the pandemic, pharmacists in some areas of shortage were overwhelmed with requests for compounding suspension from the 75 mg capsules and Roche and the FDA were asked to provide appropriate guidance on compounding larger volumes of suspension. The emergency compounding instructions were scaled up for larger volumes, tested, and then posted on Roche, FDA, and CDC websites during the pandemic. This supplement also provides updated instructions for this bulk compounding in the event of a shortage of commercial suspension. The bulk compounding instructions provide for compounding (b) (4) and the appropriate volumes of water and vehicle to produce a larger volume of 6 mg/mL suspension. These instructions are not intended for the product label but have been reviewed and will be made available on the internet as needed in periods of public health emergencies or product shortages.

In evaluating this supplement, DAVP again requested input from groups in the Office of Surveillance and Epidemiology, and their advice has been vital to the review process. Please refer to the consults provided by Scott Dallas, Safety Evaluator, DMEPA, LaShawn Griffiths, Patient Labeling Evaluator, DRISK, and Lynn Panholzer, Reviewer, DDMAC.

Medical Officer's Labeling Recommendations:

1. In all sections of the label, the concentration of Tamiflu for oral suspension or emergency compounded Tamiflu suspension from capsules will be changed to 6 mg/mL.

2. In the Dosing and Administration section of the PI, recommendations for pediatric patients using either commercial or compounded suspension will be consolidated into one dosing table displaying both treatment and prophylaxis regimens as shown below.

Table 1: Treatment and Prophylaxis Dosing of Oral TAMIFLU for Influenza For Patients 1 Year of Age and Older Based on Body Weight

Weight (kg)	Weight (lbs)	Treatment Dosing for 5 days	Prophylaxis Dosing for 10 days	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
15 kg or less	33 lbs or less	30 mg **twice** daily	30 mg **once** daily	5 mL	1 bottle	10 Capsules 30 mg
16 kg thru 23 kg	34 lbs thru 51 lbs	45 mg **twice** daily	45 mg **once** daily	7.5 mL	2 bottles	10 Capsules 45 mg
24 kg thru 40 kg	52 lbs thru 88 lbs	60 mg **twice** daily	60 mg **once** daily	10 mL	2 bottles	20 Capsules 30 mg
41 kg or more	89 lbs or more	75 mg **twice** daily	75 mg **once** daily	12.5 mL†	3 bottles	10 Capsules 75 mg

* 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.
†Delivery of this TAMIFLU for Oral Suspension dose requires administering 10 mL followed by another 2.5 mL.

3. In the Dosing and Administration section, dosing instructions for use of pediatric size Tamiflu capsules (30 and 45 mg) for patients unable to swallow capsules will be clarified.

> "…..For pediatric patients who cannot swallow capsules, TAMIFLU for oral suspension is the preferred formulation. If the oral suspension product is not available, TAMIFLU capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup, corn syrup, caramel topping, or light brown sugar (dissolved in water). If the appropriate strengths of TAMIFLU capsules are not available to mix with sweetened liquids and the oral suspension product is not available, then a pharmacist may compound an emergency supply of oral suspension from TAMIFLU 75 mg capsules."

4. The proposed labeling for compounding a suspension of Tamiflu from 75 mg capsules has been discussed with many FDA offices. Our authority to include the proposed Instructions for Pharmacists was discussed with ORP and OC prior to any specific labeling revisions being approved during the original review of these instructions. The proposed labeling provides volumes for water and vehicle for compounding the appropriate amount of 6 mg/mL suspension for pediatric patients of different weights and revised compounding instructions for pharmacists.

1. Place the specified amount of water into a polyethyleneterephthalate (PET) or glass bottle (see Table 3).
2. Carefully separate the capsule body and cap and pour the contents of the required number of TAMIFLU 75 mg capsules into the PET or glass bottle.
3. Gently swirl the suspension to ensure adequate wetting of the TAMIFLU powder for at least 2 minutes.
4. Slowly add the specified amount of vehicle to the bottle.
5. Close the bottle using a child-resistant cap and shake well for 30 seconds to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension. (Note: The active drug, oseltamivir phosphate, readily dissolves in the specified vehicles. The suspension is caused by inert ingredients of TAMIFLU capsules which are insoluble in these vehicles.)
6. Put an ancillary label on the bottle indicating "Shake Well Before Use."
7. Instruct the parent or caregiver that any unused suspension remaining in the bottle following completion of therapy must be discarded by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date on the label according to storage conditions below.

5. The instructions for larger volumes of compounded suspension are scaled up from the labeled emergency compounding instructions for pharmacists (b) (4) .

In addition, the Applicant has submitted their education and communications plan for the launch of the new strength oral suspension to the FDA review team including staff from DDMAC, DMEPA, and DRISK and discussions are in progress to optimize the plan. FDA would like to ensure information regarding the new suspension concentration and dosing recommendations is disseminated to all key stakeholders including Health Care Providers, pharmacists, and pharmaceutical buyers (including hospitals and other facilities).

Regulatory Action:

With the above listed revisions to the PI and other minor changes, this labeling supplement for Tamiflu should be approved. The proposed instructions for larger volume compounding are appropriate for use in the setting of a public health emergency or drug shortage and may be disseminated as needed but will not be included in the PI.

Linda L. Lewis, M.D.
Medical Officer Team Leader
DAVP/OAP/CDER/FDA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LINDA L LEWIS
03/21/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

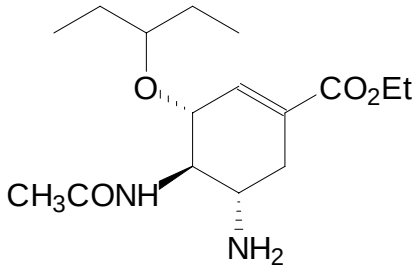
NDA 021246/S-039

CHEMISTRY REVIEW(S)

NDA 21-087
NDA 21-246
IND 53,093

Tamiflu (oseltamivir phosphate) Capsules
Tamiflu (oseltamivir phosphate) for Oral Suspension

Hoffman-La Roche



(b) (4)

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/s/

GEORGE LUNN

02/18/2011

CMC studies to support extemporaneous compounding. Note that product in SNS is NOT returnable

OFFICE ON NEW DRUG QUALITY ASSESSMENT
DIVISION OF POST-MARKETING EVALUATION, BRANCH VIII
Review of Chemistry, Manufacturing, and Controls
for the Division of Antiviral Drug Products

NDA #: 21-246 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 21-JAN-2011
TYPE: SCF-039

SUPPORTING DOC. NO.	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
299	20-SEP-2010	21-SEP-2010	21-SEP-2010
306	22-NOV-2010	22-NOV-2010	22-NOV-2010

NAME & ADDRESS OF APPLICANT: Hoffmann La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

Ms. Duane L. Voss,
Program Director, Technical Regulatory Affairs
(973) 562-3519 fax (973) 562-3700

DRUG PRODUCT NAME

Proprietary:	TAMIFLU® for Oral Suspension
Nonproprietary/USAN:	oseltamivir phosphate
Code Names/#'s:	GS-4104
Chemical Type/	3, New Formulation
Therapeutic Class:	P, Priority Review Drug

ANDA Suitability Petition/DESI/Patent Status: N/A

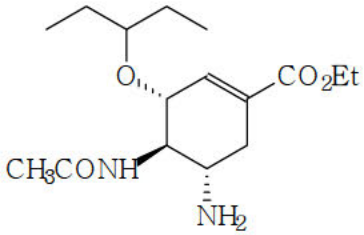
PHARMACOLOGICAL CATEGORY/INDICATION: For the treatment and prophylaxis of influenza.

DOSAGE FORM: Powder for Oral Suspension
STRENGTHS: 12mg/mL (as free base) (1.2%)
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _X_ **Rx** ___ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

(3R,4R,5S)-4-Acetylamino-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1)

Molecular Formula: $C_{16}H_{28}N_2O_4 \cdot PO_4$
Molecular Weight: 410.4 (312.4 free base) CAS Number: [204255-11-8]



(b) (4)

REMARKS/COMMENTS:

This "Supplement for Prior Approval" for NDA 21-246, originally approved 14-DEC-2000, was submitted to provide for a change in the concentration of the constituted suspension, from 12mg/mL to 6mg/mL, and a change to volumetric dosing (from mg to mL). (b) (4)

The following changes are included in this Supplement:

1. The concentration is changing from 12mg/mL to 6mg/mL.
2. The product will be dosed by volume (mL rather than mg).
3. The commercial package size (glass bottle) will change from 60mL to 100mL.
4. The child-resistant plastic closure is changing from one that required tamper-evident neckbanding to a child-resistant one that has a perforated plastic ring at its base, which breaks apart when the bottle is opened.
5. The 5mL oral dispenser will be replaced with a 10mL dispenser, with no change to the composition or supplier of the dispenser.

(b) (4)

7. The text on the bottle label and carton will be revised accordingly, and in addition, the product will be rebranded from Roche to Genentech.
8. The Package Insert is also being revised.

This supplement is OND-managed.

CONCLUSIONS & RECOMMENDATIONS: **APPROVAL**

The information submitted is adequate to support the proposed change. Approval is recommended.

(see attached electronic signature page)

Joel S. Hathaway, Ph.D.
Reviewing Chemist

cc: Orig. NDA 21-246
OND/DAVDP/ProjMgr/EThompson
ONDQA/DPA2/CMCLead/DLewis
ONDQA/DPA2/ProjMgr/JDavid
OND/DAVDP/Division File
ONDQA/DPA2/Chem/JSHathaway
ONDQA/DPA2/BranchChf/TOliver

filename: C:\Documents and Settings\hathaways\My Documents\MSWordDocs\NDA Reviews\SuppNDAs\21246\N21246r.scf.039.doc

Approval

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/s/

JOEL S HATHAWAY
01/21/2011

THOMAS F OLIVER
01/21/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021246/S-039

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration

Silver Spring, MD 20993

Division of Antiviral Products
Regulatory Project Manager Labeling Review-Prior Approval Supplement

Application Numbers: 21-087/S-056 and 21-246/S-039

Name of Drug: Tamiflu (oseltamivir phosphate) capsules and oral suspension

Applicant: Hoffmann-La Roche Inc.
Attn: Bhavini Patel
Senior Program Manager, Drug Regulatory Affairs

Submission Date: September 20, 2010

Receipt Date: September 21, 2010 (NDA 21-246; electronic) and October 29, 2010 (NDA 21-087; paper)

Amendment Dates:
November 22, 2010 (b) (4)
December 17, 2010 (communication plan)
February 11, 2011 (response to FDA request; revised labeling; carton/container labeling)
February 15, 2011 (draft communication document for review)
February 24, 2011 (response to FDA request-CMC info)
March 16, 2011 and March 18, 2011 (response to labeling comments; revised labeling; carton/container labeling)

Receipt Dates:
November 22, 2010
December 17, 2010 (submitted to NDA 21-246 only)
February 11, 2011
February 15, 2011 (submitted to NDA 21-246 only)
February 24, 2011
March 16, 2011 and March 18, 2011

Materials Reviewed:
Last approved labeling (NDA 21-087/S-057 and NDA 21-246/S-040) dated January 27, 2011 and approved February 7, 2011.

Prior Approval Supplements dated September 20, 2010 and the above amendments

Background and Summary:
To [redacted] (b) (4) improve dosing accuracy, Roche submitted Prior Approval Supplements that support a change in concentration of the Tamiflu Oral Suspension from 12mg/mL to 6mg/mL and a change to volumetric dosing (from mg to mL). Roche also changed the emergency compounding instructions and final concentration to 6mg/mL to align with the concentration of the commercially available suspension. Changes to labeling were proposed for the Package Insert, Patient Information and Carton and Container.

Review:

General:

1. Upon request, Roche eliminated the use of symbols (≥) in Highlights and in the Dosage and Administration section

2. Concentration changed throughout label from 12mg/mL to 6mg/mL for Oral Suspension and from 15mg/mL to 6mg/mL for emergency compounding final concentration

HIGHLIGHTS

1. [redacted] (b) (4)

2. Revised text under Recent Major Changes to include new Dosage and Administration sections that were revised

3. Under Dosage Forms and Strengths, revised text to read 360 mg oseltamivir and final concentration of 6 mg/mL)

FPI

1. Tables 1 and 2 were combined into one dosing table for both treatment and prophylaxis (now Table 1). Table 5 was deleted since dosing of compounded suspension is same as commercial suspension (now included in Table 1)

2. The following changes to the Dosage and Administration section were made:

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/s/

ELIZABETH G THOMPSON
03/21/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 10, 2011
To:	Debra B. Birnkrant, MD, Director Division of Anti-Viral Products
Thru:	Carol Holquist, RPh, Director Division of Medication Errors and Prevention and Analysis
From:	Scott Dallas, RPh, Safety Evaluator Division of Medication Errors and Prevention and Analysis
Subject:	Tamiflu Label and Labeling Review
Drug Name(s):	Tamiflu (oseltamivir phosphate) for oral suspension
Application Type / Number:	NDA-21246
Applicant/sponsor:	Hoffmann La Roche Inc
OSE RCM #:	2010 - 2272

Contents

1 INTRODUCTION

This review evaluates the package insert, patient information, container label and carton labeling submitted by the applicant on February 11, 2011 in support of supplement #39 for Tamiflu (oseltamivir phosphate) for oral suspension. The applicant has proposed to revise the concentration of the commercially prepared oral suspension from 12 mg/mL to 6 mg/mL, and the emergency compounded oral suspension from 15 mg/mL to 6 mg/mL.

2 METHODS AND MATERIAL REVIEWED

The label and labeling was reviewed using the principles of Failure Mode and Effects Analysis (FMEA)[1]. We reviewed the following label and labeling:

- Package Insert labeling (Appendix A)
- Patient Information labeling, lines 92-97 (Appendix B)
- Container label, 6 mg/mL after reconstitution (Appendix C)
- Carton labeling, 6 mg/mL after reconstitution (Appendix D)

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation has identified areas where information on the package insert, container label and carton labeling could be improved to minimize the potential for medication errors. We provide comments and recommendations for revisions in Section 4.1 and 4.2 that aim at reducing the risk of future medication errors.

The Division of Medication Error Prevention and Analysis would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, then please contact Project Manager, Brantley Dorch at 301-796-0150.

3.1 COMMENTS TO THE DIVISION

DMEPA has identified text in the package insert that is vulnerable to confusion and could be misinterpreted. We have deleted vulnerable text and proposed alternative language in the body of the document. In addition, we have identified

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

text that needs to be further evaluated by clinical or chemistry personnel by inserting a comment in the body of the text. (see Appendix A).

3.2 COMMENTS TO THE APPLICANT

Our assessment of the package insert, patient information, container label and carton labeling indicates that the presentation of some text is vulnerable to confusion and could result in medication errors. Therefore, we recommend revisions to the text on the package insert, patient information, container label and carton labeling.

A. Package Insert Labeling

DMEPA has recommended revisions to text and to the format of Table 1 to decrease the risk of confusion and medication errors. The recommendations are noted as a tracked change to the proposed package insert labeling.

Please ensure a line of text in the narrative portion does not end with a number when revisions are made to the package insert. Including a unit of measure, such as mg, kg, or days directly after a number may decrease the probability that the information is misinterpretation.

B. Patient Information

1. (b) (4) We note that Tamiflu has been approved for two indications of use, which includes either for the treatment or prophylaxis of influenza. (b) (4) A more inclusive phrase needs to be incorporated that would be appropriate for both indications of use. We recommend revising the phrase (b) (4) to read "prescribed dosing", so that the sentence reads "Discard any unused portion, when you are finished with your prescribed dosing of TAMIFLU."
2. Please insert the words "a dose of" in Line (b) (4) so the title reads "**How Do I Prepare a dose of TAMIFLU for Oral Suspension?**

C. Container Labels

1. Increase the prominence of the usable volume statement on the principal display panel. The order of prominence of the information needs to be the proprietary name, established name, final concentration (6 mg/mL) followed by the usable volume statement. We recommend the usable volume statement be displayed in a format similar to:

   60 mL (usable volume after reconstitution).

2. Revise the statement on the side panel to read "Shake Well before each use" by deleting the words (b) (4) from the statement.
3. We concur with your approach in utilizing a different print color to aid in differentiating the storage condition statement from the pharmacist preparation

instructions on the container label. However, we recommend revising the storage statement on the side panel to read:

Store reconstituted product as follows:
Refrigerate and discard unused portion
after 17 days, **OR**
Keep at Room Temperature and
discard unused portion after 10 days

D. Carton Labeling (trays)

1. Increase the prominence of the usable volume statement on the principal display panel and the opposing large panel of the carton. The order of prominence of the information needs to be the proprietary name, established name, final concentration (6 mg/mL) followed by the usable volume statement. We recommend the usable volume statement be displayed in a format similar to:

   60 mL (usable volume after reconstitution).

2. We recommend revising the storage statement under the section titled "Note to patients and caregivers:" to read:

   Store reconstituted product as follows:
   Refrigerate and discard unused portion
   after 17 days, **OR**
   Keep at Room Temperature and
   discard unused portion after 10 days

3. Revise the phrase (b) (4) to read "prescribed dosing", so that the sentence reads "When finished with the prescribed dosing, discard any unused portion."

4. Revise the statement that reads: (b) (4) " to "When reconstituted the usable volume of oral suspension is 60 mL, equivalent to 360 mg of oseltamivir free base. "

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/s/

SCOTT M DALLAS
03/10/2011

CAROL A HOLQUIST
03/10/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

PRE-DECISIONAL AGENCY MEMO

Date: March 3, 2011

To: Elizabeth Thompson, DAVP

From: Lynn Panholzer, PharmD, DDMAC
Michelle Safarik, PA-C, DDMAC

Re: NDA# 021087/S-056, 021246/S-039
Tamiflu® (oseltamivir phosphate) capsules and for oral suspension

As requested in your consult dated February 15, 2011, DDMAC has reviewed the draft labeling (package insert [PI], patient package insert [PPI], carton and container labeling) for Tamiflu® (oseltamivir phosphate) capsules and for oral suspension. DDMAC's comments are based on the proposed substantially complete, marked-up version of the labeling found in the EDR at \\CDSESUB1\EVSPROD\NDA021246\0012.

DDMAC's comments on the PI and PPI are provided directly in the attached, marked-up copy of the labeling. DDMAC has no comments on the carton and container labeling.

If you have any questions about DDMAC's comments on the PI please contact Lynn Panholzer at 6-0616 or at Lynn.Panholzer@fda.hhs.gov. If you have any questions about our comments on the PPI please contact Michelle Safarik at 6-0620 or at Michelle.Safarik@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
03/03/2011

MICHELLE L SAFARIK
03/03/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 30, 2010

TO: OSE

THROUGH : DAVP

FROM: Elizabeth Thompson, RPM

SUBJECT: OSE consult for Tamiflu 6mg/mL labeling supplement

APPLICATION/DRUG: NDA 21-246/S-039

On October 25, 2010, DAVP requested OSE review the Tamiflu labeling supplement for conversion from 12mg/mL to a 6mg/mL oral suspension. OSE assigned Scott Dallas (DMEPA) and Latonia Ford (DRISK). After further review of the supplement, the DAVP agreed that no DRISK review of the supplement was needed. This memo serves to make notice that only DMEPA is requested to review this supplement.

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/s/

ELIZABETH G THOMPSON
12/02/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021246/S-039

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Elizabeth Thompson, OAP/DAVP, 301-796-0824

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS: labeling and communication plan (PLEASE CHECK OFF BELOW)
2-14-11	53,093	NDA 21-087/S-056 NDA 21-246/S-039	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tamiflu	asap	Treatment of influenza	3/3/11

NAME OF FIRM:	
Hoffmann-La Roche, Inc.	PDUFA Date: 3/21/11

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☒ PACKAGE INSERT (PI)
☒PATIENT PACKAGE INSERT (PPI)
☒CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☒ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☒ LABELING REVISION

EDR link to submission:
link to recent labeling amendment/response to comments: \\CDSESUB1\EVSPROD\NDA021246\0012
link regarding communication plan: \\CDSESUB1\EVSPROD\NDA021246\0007

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling Meetings: March 3, 2011 1-2:30pm; will schedule more if needed

SIGNATURE OF REQUESTER
Elizabeth Thompson

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☒ eMAIL ☐ HAND

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ELIZABETH G THOMPSON
02/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-246/S-039
NDA 21-087/S-056

INFORMATION REQUEST

Hoffmann-La Roche, Inc.
Attention: Duane L. Voss
Program Director
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Voss:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAMIFLU (oseltamivir phosphate) Capsules and Oral Suspension.

We also refer to your submissions dated November 22, 2010 and December 17, 2010.

We are reviewing your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

Labeling Comments

Package Insert

1. Please combine Tables 1 and 2 into one dosing table displaying both treatment and prophylaxis (similar to that proposed for Table 5). Since dosing of compounded suspension is now the same as for commercial suspension, delete Table 5 and refer to the new dosing table.
2. Add "1 year and older" to title above dosing table.
3. Eliminate overlapping weights and use of symbols in dosing table (e.g., "23kg" and ">23kg" in different weight bands). You may need to provide justification for specific weight cut-offs (e.g., should cut-off be 23.1 kg or 24 kg for next weight band).
4. Eliminate the use of symbols in the Dosage and Administration subsection of the Highlights section.
5. (b) (4)
6. Please provide documentation to support the deliverable amount that can be consistently withdrawn from the bottle using an oral syringe.

7. Please include a statement below the dosing table noting that delivery of the Oral Suspension dose for patients greater than 40 kg requires administering 10 mL followed by another 2.5 mL.

Carton/Container Labeling

8. It will be important to emphasize the "new strength" of this formulation. Thus we recommend flagging the carton with the statement "New Strength" for the first six months of introducing this product into the marketplace. (b) (4) .
9. In order to further differentiate the National Drug Codes of the two oral suspension products we recommend increasing the prominence of the product identifier, 820, on the carton and container. Various methods or a combination of methods could be considered to increase the prominence, such as increasing the font size or bolding.
10. Please include a statement on the principal display panel to indicate the deliverable amount of suspension "xx mL after constitution". This information may help ensure the correct numbers of bottles are dispensed to a patient.
11. (b) (4) We recommend separating this information by creating a side panel for pharmacists and a side panel for patients and caregivers. Consider if readability of the pharmacist information could be improved by modifying the text or format to ensure the product is constituted properly and the bottle adapter is inserted properly by the pharmacist prior to being dispensed to the patient. Likewise, the information for the patient and caregiver side panel could be modified to enhance the readability. (b) (4)
12. (b) (4)
13. (b) (4)

Compounding from (b) (4) Comments (November 22, 2010 submission)

1. We concur with your proposal for further shaking studies described in Attachment 2 of your letter of November 11, 2010. However, the proposed shaking times may not be representative of shaking times normally performed by pharmacists. In order to help determine the robustness of this methodology and ensure this methodology could be employed in a real world setting then shorter shaking times need to be tested. (b) (4)

(b) (4)

2. Please also provide information to support the use of Cherry Syrup and simple syrup in this large scale compounding

Communication Plan Comments (December 17, 2010 submission)

1. In general, we agree with your planned communication strategy and will review documents submitted as quickly as possible.
2. Please note in your communications that 30 mg and 45 mg capsules are available for use in pediatric patients as well as the Oral Suspension and have not changed configuration.
3. When you provide the communication documents, please provide more details on how you will manage the take-back program and which stakeholders are eligible to use this program.
4. Other key stakeholder who should be included in the communications plan include holders of federal, state, and local stockpiles, including but not limited to the Strategic National Stockpile and the Department of Defense. Are these entities included in the general take-back program?
5. We encourage you to engage with health literacy groups and public health agencies involved in influenza recommendations prior to launch of the general communication plan as they may have useful advice on best practices for changing dosing recommendations for a widely used product.

If you have questions, call me at (301) 796-0824 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Elizabeth Thompson, M.S.
LT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

ELIZABETH G THOMPSON
01/05/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Elizabeth Thompson, RPM x6-0824, DAVP/OAP	
DATE: October 25, 2010	IND NO.: 53,093	NDA NO.: 21-246	TYPE OF DOCUMENT: Prior Approval Labeling Supplement	DATE OF DOCUMENT: 9/20/10
NAME OF DRUG: Tamiflu	PRIORITY CONSIDERATION: asap		CLASSIFICATION OF DRUG: Treatment/prophylaxis of influenza	DESIRED COMPLETION DATE: December 25, 2010

NAME OF FIRM: Hoffmann-La Roche

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: DAVP would like OSE to review the PAS for Tamiflu. DMEPA(Scott Dallas/Carol Holquist) has been involved in the labeling issues regarding Tamiflu in the past. The PAS includes a change in concentration of the oral suspension from 12mg/ml to 6mg/ml. DRISK may want to be involved in the review as well. Please let RPM know who the assigned DRISK reviewer is.

This supplement is located on the EDR: \\CDSESUB1\EVSPROD\NDA021246\0000

This supplement has a 6 month goal date of March 20, 2011; however, the DAVP would like to take action sooner. RPM will schedule meetings to discuss and invite assigned reviewers from OSE. Linda Lewis is MO; George Lunn is chemistry reviewer.

SIGNATURE OF REQUESTER Elizabeth Thompson	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

ELIZABETH G THOMPSON
10/25/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-246/S-039

PRIOR APPROVAL SUPPLEMENT

Hoffmann-La Roche Inc.
Attention: Duane Voss
Program Director, Technical Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms. Voss:

We have received your September 20, 2010, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21-246

SUPPLEMENT NUMBER: 039

PRODUCT NAME: TAMIFLU (oseltamivir phosphate) for Oral Suspension

DATE OF SUBMISSION: September 20, 2010

DATE OF RECEIPT: September 21, 2010

This supplemental application proposes the following changes:

- Change in concentration of the constituted suspension from 12 mg/mL to 6 mg/Ml
- Change to volumetric dosing (from mg to mL)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 19, 2010 in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be March 21, 2011.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-0824.

Sincerely,

{See appended electronic signature page}

Elizabeth Thompson, M.S.
LT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

ELIZABETH G THOMPSON
10/15/2010