CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021087/S-048

Trade Name: **TAMIFLU**

Generic Name: **Oseltamivir Phosphate**

Sponsor: **Hoffmann-La Roche Inc.**

Approval Date: 02/22/2010

Indications: 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.

• Prophylaxis of influenza in patients 1 year and older.

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APPLICATION NUMBER:

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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-048 and S-049
NDA 21-246/S-034 and S-035

SUPPLEMENT APPROVAL

Hoffmann-La Roche Inc.
Attention: Sukirti D. Mukheja, B.S., Pharm.D.
Senior Program Manager
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Mukheja:

Please refer to your supplemental new drug applications dated May 29, 2009 and August 7, 2009, received June 1, 2009 and August 10, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TAMIFLU (oseltamivir phosphate) 30 mg, 45 mg and 75 mg capsules and 12 mg/mL oral suspension.

We also acknowledge receipt of your submissions dated December 16, 2009, December 17, 2009, January 11, 2010, January 15, 2010, January 18, 2010, February 1, 2010, February 5, 2010 and February 22, 2010.

These "Prior Approval" supplemental new drug applications provide for the conversion of the package insert to PLR and incorporating labeling changes based on data from the following clinical studies:

- NV20235: "A randomized, controlled, multi-center trial of oseltamivir versus placebo for the seasonal prophylaxis of influenza in immunocompromised patients"

- NV20236: "An open label trial to treat children ages 1-12 for seasonal prophylaxis during influenza season"

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

Within 14 days from the date of this letter, please amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format that includes the changes approved in this supplemental application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see 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 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 an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

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 Robert G. Kosko, Jr., Regulatory Project Manager, at (301) 796-3979 or at the Division's main number (301) 796-1500.

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

Enclosure
Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21246	SUPPL-35	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML
NDA-21246	SUPPL-34	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML
NDA-21087	SUPPL-49	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21087	SUPPL-48	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES

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
02/22/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021087/S-048

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----------

Indications and Usage (1.3)	2/2010
Dosage and Administration (2.3, 2.4, 2.7)	2/2010
Warnings and Precautions (5.3, 5.4)	2/2010

---------- 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): 75 mg twice daily for 5 days
- Pediatric patients (≥1 year): Based on weight twice daily for 5 days
- Renally impaired patients (creatinine clearance 10-30 mL/min): Reduced to 75 mg once daily for 5 days (2.4)

Prophylaxis of influenza (2.3)

- Adults and adolescents (≥13 years): 75 mg once daily for at least 10 days
  - Community outbreak: 75 mg once daily for up to 6 weeks
- Pediatric patients (≥1 year): 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): Reduced 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: 300 mg oseltamivir base (constituted to a final concentration of 12 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 Roche at 1-800-526-6367 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: 2/2010

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 Considerations

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.

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.

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. TAMIFLU for oral suspension may also be used by patients who cannot swallow a capsule. 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.

Table 1 Oral Dose of TAMIFLU for Treatment of Influenza in Pediatric Patients by Weight

Body Weight (kg)	Body Weight (lbs)	Recommended Dose for 5 Days	Number of Bottles of TAMIFLU for Oral Suspension to Dispense for a 5-Day Regimen	Number of TAMIFLU Capsules to Dispense for a 5-Day Regimen
≤15 kg	≤33 lbs	30 mg twice daily	1	10 TAMIFLU Capsules (30 mg)
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg twice daily	2	10 TAMIFLU Capsules (45 mg)
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg twice daily	2	20 TAMIFLU Capsules (30 mg)
>40 kg	>88 lbs	75 mg twice daily	3	10 TAMIFLU Capsules (75 mg)

An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser provided is lost or damaged, another dosing syringe or other device may be used to deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for >15 to 23 kg, 5 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

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. Safety has been demonstrated for up to 12 weeks in immunocompromised patients. The duration of protection lasts for as long as dosing is continued.

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 2. TAMIFLU for oral suspension may also be used by patients who cannot swallow a capsule. 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.

Table 2 Oral Dose of TAMIFLU for Prophylaxis of Influenza in Pediatric Patients by Weight

Body Weight (kg)	Body Weight (lbs)	Recommended Dose for 10 Days	Number of Bottles of TAMIFLU for Oral Suspension to Dispense for a 10-Day Regimen	Number of TAMIFLU Capsules to Dispense for a 10-Day Regimen
≤15 kg	≤33 lbs	30 mg once daily	1	10 TAMIFLU Capsules (30 mg)
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg once daily	2	10 TAMIFLU Capsules (45 mg)
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg once daily	2	20 TAMIFLU Capsules (30 mg)
>40 kg	>88 lbs	75 mg once daily	3	10 TAMIFLU Capsules (75 mg)

An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser provided is lost or damaged, another dosing syringe or other device may be used to deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for >15 to 23 kg, 5 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

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 Warnings and Precautions (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 **23 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 (12 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 TAMIFLU Capsules (Final Concentration 15 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 (12 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 (15 mg/mL) from TAMIFLU capsules 75 mg using either of two vehicles: Cherry Syrup (Humco®) or Ora-Sweet® SF (sugar-free) (Paddock Laboratories). 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 3).

Table 3 Volume of an Oral Suspension (15 mg/mL) Needed to be Compounded Based Upon the Patient's Weight

Body Weight (kg)	Body Weight (lbs)	Total Volume to Compound per Patient (mL)
≤15 kg	≤33 lbs	30 mL
>15 to 23 kg	>33 to 51 lbs	40 mL
>23 to 40 kg	>51 to 88 lbs	50 mL
>40 kg	>88 lbs	60 mL

Second, determine the number of capsules and the amount of vehicle (Cherry Syrup or Ora-Sweet SF) that are needed to prepare the total volume (calculated from Table 3: 30 mL, 40 mL, 50 mL, or 60 mL) of compounded oral suspension (15 mg/mL) (see Table 4).

Table 4 Number of TAMIFLU 75 mg Capsules and Amount of Vehicle (Cherry Syrup OR Ora-Sweet SF) Needed to Prepare the Total Volume of a Compounded Oral Suspension (15 mg/mL)

Total Volume of Compounded Oral Suspension to be Prepared	**30 mL**	**40 mL**	**50 mL**	**60 mL**
Required 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)
Required Volume of Vehicle Cherry Syrup (Humco) **OR** Ora-Sweet SF (Paddock Laboratories)	29 mL	38.5 mL	48 mL	57 mL

Third, follow the procedure below for compounding the oral suspension (15 mg/mL) from TAMIFLU capsules 75 mg:

a) Carefully separate the capsule body and cap and transfer the contents of the required number of TAMIFLU 75 mg capsules into a clean mortar.
b) Triturate the granules to a fine powder.
c) Slowly add a small amount of vehicle (approximately 1 mL per 6 capsule contents) to the triturated TAMIFLU powder and levigate well with the pestle (approximately 2-3 minutes) to a smooth mass. Continue adding very slowly the remainder of one-third (1/3) of the total amount of vehicle in 3 small portions to the mortar while triturating with the pestle until a uniform suspension is achieved each time.
d) Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
e) Add the second one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar by a triturating motion, and transfer the vehicle into the bottle.
f) Repeat the rinsing with the remaining one-third (1/3) of the vehicle.
g) Close the bottle using a child-resistant cap.
h) Shake well 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.)
i) Put an ancillary label on the bottle indicating "Shake Gently Before Use." (Note: This compounded suspension should be gently shaken prior to administration to minimize the tendency for air entrapment, particularly with the Ora-Sweet SF preparation.)
j) 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.
k) Place an appropriate expiration date on the label according to storage conditions below.

Storage of the 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 amber glass and amber 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 (15 mg/mL)

Refer to Table 5 for the proper dosing instructions for the pharmacy label.

Note: This compounding procedure results in a 15 mg/mL suspension, which is different from the commercially available TAMIFLU for oral suspension, which has a concentration of 12 mg/mL.

Table 5 Dosing Chart for Pharmacy-Compounded Suspension from TAMIFLU Capsules 75 mg

Body Weight (kg)	Body Weight (lbs)	Dose (mg)	Volume per Dose (15 mg/mL)	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
≤15 kg	≤33 lbs	30 mg	2 mL	2 mL two times a day	2 mL once daily
>15 to 23 kg	>33 to 51 lbs	45 mg	3 mL	3 mL two times a day	3 mL once daily
>23 to 40 kg	>51 to 88 lbs	60 mg	4 mL	4 mL two times a day	4 mL once daily
>40 kg	>88 lbs	75 mg	5 mL	5 mL two times a day	5 mL once daily

Note: 1 teaspoon = 5 mL

Consider dispensing the suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (2 mL, 3 mL, 4 mL, or 5 mL) on the oral syringe for each patient. The dosing device dispensed with the commercially available TAMIFLU for oral suspension should NOT be used with the compounded suspension since the two formulations have different final concentrations.

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: 12 mg/mL (final concentration)

- White powder blend for constitution to a white tutti-frutti–flavored suspension. Each bottle delivers 25 mL of suspension equivalent to 300 mg oseltamivir base.

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 which can include events such as hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving TAMIFLU. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made but they appear to be uncommon based on TAMIFLU usage data. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of TAMIFLU to these events has not been established. Closely monitor patients with influenza for signs of abnormal behavior. If neuropsychiatric symptoms occur, evaluate the risks and benefits of continuing treatment for each patient.

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 6. 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 6). 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 6 Most Frequent Adverse Events in Studies in Naturally Acquired Influenza in Subjects 13 Years of Age and Older

	Treatment				Prophylaxis			
Adverse Event[a]	**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 7. 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 7).

Table 7 Most Frequent Adverse Events Occurring in Children Aged 1 to 12 Years in Studies in Naturally Acquired Influenza

	Treatment Trials[b]				**Household Prophylaxis Trial[c]**			
Adverse Event[a]	**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 7 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

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 twofold 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, 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 patients.

The safety of TAMIFLU in geriatric subjects has been established in clinical studies which 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)]*.

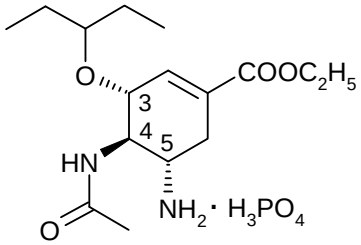
10 OVERDOSAGE

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 12 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 8).

Table 8 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 9.

Table 9 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 of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of oseltamivir carboxylate required for inhibition of influenza virus 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 relationship between the antiviral activity in cell culture 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. Genetic analysis of these isolates showed that reduced susceptibility to oseltamivir carboxylate is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both. Resistance substitutions selected in cell culture in neuraminidase are I222T and H274Y in influenza A N1 and

I222T and R292K in influenza A N2. Substitutions E119V, R292K, and R305Q have been selected in avian influenza A neuraminidase N9. Substitutions A28T and R124M have been selected in the hemagglutinin of influenza A H3N2 and substitution H154Q in the hemagglutinin of a reassortant human/avian virus H1N9.

In clinical studies in the treatment of naturally acquired infection with influenza virus, 1.3% (4/301) of posttreatment isolates in adult patients and adolescents, and 8.6% (9/105) in pediatric patients aged 1 to 12 years showed emergence of influenza variants with decreased neuraminidase susceptibility in cell culture to oseltamivir carboxylate. Substitutions in influenza A neuraminidase resulting in decreased susceptibility were H274Y in neuraminidase N1 and E119V and R292K in neuraminidase N2. Insufficient information is available to fully characterize the risk of emergence of TAMIFLU resistance in clinical use.

In clinical studies of postexposure and seasonal prophylaxis in immunocompetent subjects, determination of resistance by population nucleotide sequence analysis was limited by the low overall incidence rate of influenza infection and prophylactic effect of TAMIFLU.

Cross-resistance

Cross-resistance between zanamivir-resistant influenza mutants and oseltamivir-resistant influenza mutants has been observed in cell culture. Due to limitations in the assays available to detect drug-induced shifts in virus susceptibility, an estimate of the incidence of oseltamivir resistance and possible cross-resistance to zanamivir in clinical isolates cannot be made. However, two of the three oseltamivir-induced substitutions (E119V, H274Y and R292K) in the viral neuraminidase from clinical isolates occur at the same amino acid residues as two of the three substitutions (E119G/A/D, R152K, and R292K) observed in zanamivir-resistant virus.

Immune Response

No influenza vaccine 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, 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 (AUC0-24h) 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 and 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 which 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 - 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 for constitution to a white tutti-frutti–flavored suspension. Available in glass bottles containing approximately 33 mL of suspension after constitution. Each bottle delivers 25 mL of suspension equivalent to 300 mg oseltamivir base. Each bottle is supplied with a bottle adapter and 1 oral dispenser (NDC 0004-0810-95).

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.

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 13 g 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.

Humco® is a registered trademark of Humco Holding Group, Inc.
Ora-Sweet® SF is a registered trademark of Paddock Laboratories

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TUCOS_640796_PI_012010_N(1)

Rev. February 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021087/S-048

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 22, 2010
From	Linda L. Lewis, M.D. Medical Team Leader Division of Antiviral Products
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	21-087/S-048, S-049 21-246/S-034, S-035
Applicant	Hoffman-LaRoche Inc.
Date of Submission	August, 2009
PDUFA Goal Date	February 10, 2010
Proprietary Name / **Established (USAN) names**	Tamiflu® (oseltamivir phosphate)
Dosage forms / Strength	Tablets, 75 mg Dry Powder for Oral Suspension, 12 mg/mL
Proposed Indication(s)	1. (b) (4)
Recommended:	*Approval, with modifications in proposed labeling as noted*

1. Introduction

Tamiflu is currently approved for treatment of influenza in otherwise healthy adults and pediatric patients > 1 year of age. It is also approved for prophylaxis of influenza after a known exposure (post-exposure prophylaxis) in adult and pediatric patients for 10 days of dosing and for prophylaxis during a community outbreak (seasonal prophylaxis) in adults, including elderly adults, for up to 6 weeks of dosing. As stated in the Tamiflu label, the effects of prophylaxis appear to extend for the duration of dosing. At the time of the earliest prophylaxis indication approval in November, 2000, the FDA issued a postmarketing commitment (PMC) for Roche to evaluate Tamiflu as prophylaxis and treatment in immunocompromised patients. Immunocompromised patients may be more likely to acquire influenza and are more likely to develop severe manifestations of infection and additionally, may not mount appropriate responses to influenza vaccine. Therefore, they represent a subpopulation that might uniquely benefit from prophylaxis.

The post-exposure prophylaxis indication for Tamiflu was extended to pediatric patients on the basis of a randomized, controlled study of households in which one household member developed influenza. At the time of that approval in December, 2005, the FDA issued another PMC for Roche to evaluate the safety of longer duration prophylaxis in pediatric patients. The review team believed that an efficacy study of seasonal prophylaxis in pediatric patients was not needed but that efficacy could be extrapolated based on the similarity of responses in pediatric and adult patients in both treatment and post-exposure prophylaxis. However, evidence of safety of the longer duration of dosing was requested in a cohort of pediatric patients.

2. Background

The Applicant submitted the protocol for Study NV20235: *A randomized, controlled, multi-center trial of oseltamivir versus placebo for the seasonal prophylaxis of influenza in immunocompromised patients*, as a Special Protocol Assessment in May, 2006, and requested that the protocol be considered to fulfill the prophylaxis element of the PMC for evaluation of immunocompromised patients. Roche asked for agreement on study design, endpoints, and population. DAVP provided input and agreed in principle that the study, if successfully completed, would fulfill part of the PMC. We agreed that solid organ transplant (SOT) patients and hematopoietic stem cell transplant (HSCT) patients provided adequate representation of the variety of immunocompromised patients. The current sNDA contains the final study report for Study NV20235 and requests the study results be incorporated into the Tamiflu label. The Applicant proposes that the Tamiflu label include specific prophylaxis dosing recommendations for immunocompromised patients.

The Applicant also submitted the protocol for Study NV20236: *An open label trial to treat children ages 1-12 for seasonal prophylaxis during influenza season*, for review in May, 2006. This study was completed and the final study report was submitted to NDA 21-246 to fulfill

the PMC for evaluation of the safety of seasonal prophylaxis in pediatric patients in May, 2008. The study was reviewed by Dr. Julie-Ann Crewalk and her Clinical Review was electronically archived June 11, 2009. Roche was subsequently notified that the PMC was considered fulfilled and labeling incorporating the study results was requested. The Applicant elected to submit labeling related to Study NV20236 with the current supplement containing the results of Study NV20235.

The final element of the PMC to evaluate treatment of influenza in immunocompromised patients is in progress. The protocol for Study NV20234: *An open-label randomized, stratified, dose comparison, multi-center trial of oseltamivir for the treatment of influenza in immunocompromised patients*, was submitted at the same time as the two studies included in this supplement. Because of the emergence of resistance to Tamiflu among isolates of seasonal influenza A H1N1 in Europe in 2007 and the subsequent global spread of this strain, completion of Study NV20234 has been delayed and the study required modification.

For administrative purposes, review of NDA 21-087, SLR-048 (and NDA 21-246, SLR-034) is being incorporated into this regulatory action. SLR-048 provides for the conversion of the Tamiflu label into the format required by the Physician Labeling Rule (PLR). The PLR format contains similar content as the previous Tamiflu label but mandates a specific structure for the label. In addition, SLR-048 contains a reanalysis of an earlier juvenile rat toxicology study and revised labeling related to this study.

3. CMC/Device

The Applicant provided additional stability data as part of this supplement and proposes minor changes to the allowed storage conditions for Tamiflu for Oral Suspension. These data were reviewed by Dr. Joel S. Hathaway, the CMC Reviewer, and the relevant labeling revisions were acceptable.

4. Nonclinical Pharmacology/Toxicology

In NDA 21-087/SLR-048, the Applicant provides a reanalysis of a previously submitted juvenile rat toxicology study. Previously submitted juvenile rat studies identified substantially increased mortality in newborn rats compared to older juvenile rats and adult rats. One study also identified markedly increased concentrations of the pro-drug, oseltamivir phosphate, in the brain tissue of the newborn animals. The sponsor hypothesized that the immature blood-brain barrier of the newborn rats allowed excess penetration of oseltamivir phosphate and the increased levels or pro-drug might contribute to the increased mortality. Concern about the potential impact of an immature blood-brain barrier in human infants toward toxicity led the Applicant to terminate their evaluation of Tamiflu as treatment for influenza in infants < 1 year of age.

When the key juvenile rat toxicology study was initially submitted in 2002, the results were incorporated into the Tamiflu label. However, a follow-up juvenile rat study conducted by the

NIH did not confirm the earlier findings of increased levels of oseltamivir phosphate in brain tissue. The Applicant subsequently retested blood and tissue samples from the key juvenile rat study and identified a miscalculation in the brain oseltamivir levels in the original study. The new findings cast significant doubt on the theory that an immature blood-brain barrier contributed to the juvenile rat toxicity and mortality, although an alternate explanation was not provided. In S-048, the Applicant has submitted the revised results of the juvenile rat study and asked for revision in the labeling describing the study. For a more complete description of the resubmitted juvenile rat toxicology study, please see the Pharmacology/Toxicology Review by Dr. Ita Yuen.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant did not provide any new clinical pharmacology data with this supplement. The two studies on which labeling is based used doses previously approved for prophylaxis in other patient populations or other settings.

6. Clinical Microbiology

Both of the studies described in this efficacy supplement resulted in relatively few infected subjects in whom resistance was assessed. In Study NV20236, there were no subjects acquiring influenza while receiving Tamiflu from whom isolates were available for resistance testing. Among the small number of subjects in Study NV20235 who had laboratory-confirmed influenza, 5 subjects had influenza A/H1N1 or A/unknown subtype isolates available for resistance testing. Two of the tested isolates demonstrated genotypic resistance to Tamiflu and had the H275Y substitution associated with Tamiflu resistance (one subject receiving placebo and one receiving Tamiflu). In this study, the number of isolates tested was too small to make any definitive conclusions regarding rates of resistance in this population.

For a more complete description of the virology assessments conducted as part of the review of Study NV20235 in SE-049, please refer to the Microbiology Review submitted by Dr. Damon Deming.

7. Clinical/Statistical- Efficacy

Study 20236 was an open-label, single arm, multi-center trial to evaluate the safety of Tamiflu for seasonal prophylaxis in pediatric patients > 1 year of age. The study enrolled pediatric subjects who were considered to be at high risk for increased morbidity and mortality from influenza or at risk of infecting other family members at increased influenza risk. Subjects were excluded from study if they had a rapid influenza test positive at screening or symptoms consistent with influenza at screening. A total of 52 subjects 1 through 12 years of age were enrolled and received daily doses of Tamiflu for 6 weeks at the doses approved for post-exposure prophylaxis. Nose and throat swabs for viral culture and influenza RT-PCR were

obtained at any time a subject had symptoms of illness and influenza antibody titers were measured at baseline, end of treatment, and end of follow-up. During the course of the study, 10 subjects reported feeling unwell and had samples obtained for virologic testing; none were positive for influenza. A total of 6 subjects had $\geq$ 4-fold rise in influenza antibody titer through the end of study follow-up; 4 of these were asymptomatic and 2 had some symptoms but did not meet the protocol-defined criteria for symptomatic influenza. Two of the subjects with $\geq$ 4-fold rise in influenza antibody titer had elevated titers at baseline, making it difficult to interpret the results of serologic testing in this population. The Applicant did not make specific conclusions regarding efficacy of Tamiflu prophylaxis on the basis of this study.

Study NV20235 was designed as a randomized, double-blind, prospective, multi-center trial comparing Tamiflu to placebo for prophylaxis of influenza in solid organ (kidney, liver or kidney and liver) transplant recipients (SOT) and hematopoietic stem cell transplant recipients (HSCT). Participants were required to be stable post-transplant, > 1 year of age, have no symptoms of influenza and have a negative rapid test for influenza at screening. Subjects received daily doses of Tamiflu recommended for approved prophylaxis indications for up to 12 weeks, then were followed an additional 4 weeks after treatment ended. Subjects were evaluated for flu-like symptoms at every scheduled visit and encouraged to return to clinic whenever they experienced symptoms. Nasal and throat swabs were collected for viral culture and RT-PCR at any ill visits. The primary efficacy endpoint for this study was the occurrence of laboratory-confirmed, clinical influenza defined as fever > 37.2^{o}C plus symptoms of cough and/or coryza on the same day (from at least the fourth day of study meds) plus laboratory evidence of influenza by virus culture or $\geq$ 4-fold rise in influenza antibody titer. The key secondary endpoint analysis was a comparison of the number of subjects in each treatment arm with RT-PCR-confirmed, clinical influenza in subjects not shedding virus at the time of study enrollment. Multiple other secondary endpoints included assessment of individual and combined laboratory methods of influenza diagnosis, with or without different individual and combined symptoms.

A total of 475 subjects were enrolled and randomized, 238 to receive Tamiflu and 237 to receive placebo. The treatment arms were balanced in terms of gender, age, race and ethnic background, and type of transplant. More than 60% of subjects in both arms were kidney transplant recipients. Among the 87 HSCT recipients, the median time since transplant among those randomized to Tamiflu was slightly shorter, 367 days compared to 424 days for placebo subjects. Among the SOT recipients, the median time since transplant was longer for Tamiflu subjects, 1372 days compared to 1110 days for placebo subjects. Because most subjects were beyond the most critical period of immunosuppression post-transplant, the effect of this difference is difficult to determine. About 40% of subjects in both treatment arms received influenza vaccine prior to entering the study.

The FDA Review Team confirmed the Applicant's efficacy analyses. In the primary efficacy analysis, the Applicant identified 7/238 (3%) placebo subjects and 5/237 (2%) Tamiflu subjects with laboratory-confirmed, clinical influenza as defined in the protocol. The difference between the two arms was not statistically significant in this analysis. At the time of the pre-NDA meeting with the Applicant, the FDA Review Team agreed that the most relevant analyses were those that excluded subjects who were shedding influenza virus at the

time of study enrollment (by culture or RT-PCR). If the primary endpoint was analyzed using the population not infected at baseline (excluding 12 subjects with positive culture or RT-PCR), 7 (3%) placebo subjects had confirmed influenza compared to 4 (2%) Tamiflu subjects. The difference in rate of laboratory-confirmed, clinical influenza is still not significantly different between the two arms. The Applicant proposed that serologic confirmation of influenza in this population was not reliable and that laboratory confirmation by RT-PCR was the most appropriate method. The Applicant's key secondary analysis evaluating RT-PCR-confirmed clinical influenza among subjects not infected at baseline identified 7/231 (3%) placebo subjects compared to 1/232 (< 1%) Tamiflu subjects. This comparison was statistically significantly different at p=0.03.

The Clinical Review performed by Dr. Vargas-Kasambira and the Statistical Review performed by Dr. Thomas Hammerstrom describe the efficacy analyses in more detail and describe some of the difficulties in interpreting the efficacy data for Study NV20235 presented in this supplement. As previously noted, the clinical study report submitted for Study NV20236 was reviewed by Dr. Crewalk and archived on June 11, 2009. Study NV20236 was intended as a safety study and was not designed to evaluate efficacy.

8. Safety

Both Studies NV20235 and NV20236 evaluated the safety of seasonal prophylaxis, for 12 weeks in immunocompromised subjects and for 6 weeks in at-risk pediatric patients, respectively. All subjects who were enrolled and had any post-enrollment safety data were included in the safety analyses.

Study NV20236 was specifically designed to collect safety data on pediatric subjects 1 through 12 years of age receiving Tamiflu prophylaxis for a period of 6 weeks. Of the 52 subjects enrolled, 49 had safety data available for review and 41 completed the study treatment and follow-up. Three of the subjects who withdrew prematurely from study cited the taste of the medicine as one of the reasons for withdrawal. Two subjects withdrew because of adverse events. One of these subjects developed oral mucosal blistering on Day 4 of treatment. The event was not considered related to study drug but another etiology was not identified. The other subject reported nausea on Day 2 and "feeling unwell" and not sleeping well on Day 4 of treatment. These events were considered probably related to study drug. The most commonly reported adverse events included: nausea, vomiting, otitis media, and tonsillitis, all of which were reported in 2 subjects. No clinically significant laboratory abnormalities were identified in any subject during the study. No deaths or serious adverse events were reported during the study.

In Study NV20235, all 475 subjects enrolled received at least one dose of study drug and had post-baseline data. Two subjects enrolled in the study died after being discontinued from study drug; both were randomized to placebo. In both cases, death was considered due to underlying malignancy (relapsed acute myeloid leukemia and septic shock in the setting of metastatic malignancy). Clearly, neither of these deaths could be attributed to either Tamiflu or influenza. Nonfatal serious adverse events were consistent with the underlying condition of

this population and not qualitatively different across treatment arms although there were numerically more serious adverse events among placebo subjects. A total of 51 subjects (33 placebo and 18 Tamiflu) withdrew from the study prematurely. Fourteen placebo subjects and 7 Tamiflu subjects withdrew because of adverse events. Of the 7 Tamiflu subjects who withdrew because of adverse events, 3 were considered possibly related to study drug (anxiety, amnesia, and dyspepsia). As in previous Tamiflu studies, the most commonly reported adverse events were gastrointestinal events but in Study NV20235 a similar proportion of subjects in both arms reported GI events (22% among placebo subjects and 21% among Tamiflu subjects). Table 1 shows the rates of reported adverse events for commonly reported events.

Table 1: Summary of On Treatment Adverse Events with an Incidence Rate of at least 2% by Trial Treatment

Adverse Event (Preferred Term)	Placebo N=237	Oseltamivir N=238
Diarrhea	18 (8%)	15 (6%)
Headache	10 (4%)	11 (5%)
Nausea	9 (4%)	13 (5%)
Fatigue	6 (3%)	12 (5%)
Hypertension	10 (4%)	9 (4%)
Upper respiratory tract infection	9 (4%)	8 (3%)
Vomiting	6 (3%)	9 (4%)
Nasopharyngitis	5 (2%)	9 (4%)
Peripheral edema	6 (3%)	6 (3%)
Abdominal pain	5 (2%)	5 (2%)
Dizziness	5 (2%)	5 (2%)
Cough	8 (3%)	2 (<1%)
Dyspnea	5 (2%)	3 (1%)
Pyrexia	5 (2%)	3 (1%)
Bronchitis	6 (3%)	1 (<1%)
Gastroenteritis	2 (<1%)	5 (2%)
Oropharyngeal pain	5 (2%)	1 (<1%)

Taken from Clinical Review conducted by Dr. Tafadzwa Vargas-Kasambira.

In general, the pattern of reported adverse events in both Studies NV20235 and 20236 were consistent with that reported in other treatment and prophylaxis trials of Tamiflu and no new safety signals were identified. For additional details of the safety analyses for these studies, please refer to the Clinical Reviews conducted by Drs. Vargas-Kasambira and Crewalk.

9. Advisory Committee Meeting

The review and approval of this supplement did not warrant convening an Advisory Committee meeting.

10. Pediatrics

The Applicant has had an on-going pediatric development program for Tamiflu for both treatment and prophylaxis of influenza. Study NV20235 was open to pediatric patients but very few were enrolled (18 subjects 1 to 12 years of age). Study NV20236 enrolled only pediatric patients 1 to 12 years of age and provides a reasonable safety database for the duration of dosing previously recommended for seasonal prophylaxis (6 weeks). Efficacy of Tamiflu as seasonal prophylaxis in pediatric patients can be extrapolated from adult efficacy in this setting based on the similarity of treatment responses in adult and pediatric patients and the similarity of response to post-exposure prophylaxis.

The current supplement does not trigger additional pediatric PMCs under the provisions of the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues raised with this application.

12. Labeling

Summaries of the safety and efficacy results of Study NV20235 will be incorporated into the package insert (PI) in the Adverse Reactions section (Section 6.1) and the Clinical Studies section under the heading Treatment Beyond 48 Weeks (Section 14.2). (b) (4) a description of both the primary and key secondary endpoint analyses and a summary of the safety profile will be included in the label.

Study NV20236 provides adequate safety data to include a statement about the safety profile of seasonal prophylaxis in pediatric patients and remove the statement that seasonal prophylaxis has not been evaluated in this age group. Dosing duration up to 6 weeks for seasonal prophylaxis will be included in the label, as efficacy can be extrapolated from larger, randomized clinical trials in other populations.

The Applicant submitted a labeling supplement (S-048) that includes revisions in the description of the juvenile animal toxicology study previously included in the label. It appears appropriate to remove the statement in the label referring to potential toxicity related to an immature blood-brain barrier.

13. Recommendations/Risk Benefit Assessment

I concur with the primary review team's recommendation to approve this efficacy supplement with the agreed upon revisions to the PI. While Study NV20235 failed to reach its primary efficacy endpoint, the data presented in this submission suggest that Tamiflu has benefit as prophylaxis in immunocompromised patients. Many experts identify RT-PCR as the method of choice for diagnosing influenza in this patient population in spite of the assay's inability to distinguish replicating virus from non-viable viral material. The study had the misfortune to be conducted during two influenza seasons that were relatively mild. The very low rate of influenza in the study population (eg, the placebo group) made it extremely difficult to show a statistically significant difference in the rate of laboratory-confirmed, clinical influenza in those subjects receiving Tamiflu. (b) (4) Study NV20235 represents some evidence of benefit as captured in the key secondary endpoint and the study description should be included in labeling so Health Care Providers can weigh the risks and benefits of using Tamiflu prophylaxis in their at-risk immunocompromised patients.

Both Studies NV20235 and 20236 confirm the acceptable safety profile of Tamiflu as prophylaxis. Tamiflu was discontinued because of adverse events in a small number of subjects receiving the drug for up to 12 weeks in NV20235 and generally had an acceptable safety profile in this population who were receiving a variety of other medications for serious underlying conditions. Study NV20235 represents the longest controlled prophylaxis study submitted thus far in the Tamiflu development program and enrolled potentially the most complex patient population in terms of underlying illness but no new safety signals were identified.

The characteristics of Tamiflu use in immunocompromised patients provide a favorable risk/benefit assessment for Tamiflu as prophylaxis for up to 12 weeks during influenza season based primarily on the favorable safety profile and to a lesser degree on the more limited evidence of reduction in infections identified by RT-PCR. Similarly, based on the acceptable safety data and extrapolating efficacy from other prophylaxis studies, Tamiflu may be useful for seasonal prophylaxis of influenza in pediatric patients. No additional Postmarketing requirements or Postmarketing Commitments are recommended. No specific changes to the Patient Package Insert are recommended.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21246	SUPPL-34	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML
NDA-21087	SUPPL-48	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21087	SUPPL-49	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21246	SUPPL-35	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML

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/s/

LINDA L LEWIS
02/22/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021087/S-048

CHEMISTRY REVIEW(S)

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 #: 21-087
21-246 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 23-FEB-2010

SUBMISSION/TYPE	SDN	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
21-087/SLR-048	364	29-MAY-2009	01-JUN-2009	10-JUN-2009
21-087/SLR-048(C)	404	18-JAN-2010	18-JAN-2010	18-JAN-2010
21-087/SLR-048(C)	406	01-FEB-2010	01-FEB-2010	01-FEB-2010
21-087/SES-049	378	07-AUG-2009	10-AUG-2009	10-AUG-2009
21-087/SES-049(C)	405	18-JAN-2010	18-JAN-2010	18-JAN-2010
21-087/SES-049(C)	408	01-FEB-2010	01-FEB-2010	01-FEB-2010
21-246/SLR-034	237	29-MAY-2009	01-JUN-2009	10-JUN-2009
21-246/SLR-034(C)	265	18-JAN-2010	18-JAN-2010	18-JAN-2010
21-246/SLR-034(C)	270	01-FEB-2010	01-FEB-2010	01-FEB-2010
21-246/SES-035	249	07-AUG-2009	10-AUG-2009	10-AUG-2009
21-246/SES-035(C)	266	18-JAN-2010	18-JAN-2010	18-JAN-2010
21-246/SES-035(C)	269	01-FEB-2010	01-FEB-2010	01-FEB-2010

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

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

DRUG PRODUCT NAME

Proprietary:	TAMIFLU® Capsules
Nonproprietary/USAN:	oseltamivir phosphate
Code Names/#'s:	
Chemical Type/	Ethyl ester prodrug
Therapeutic Class:	Antiviral; influenza virus neuraminidase inhibitor

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

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

DOSAGE FORM: Capsules

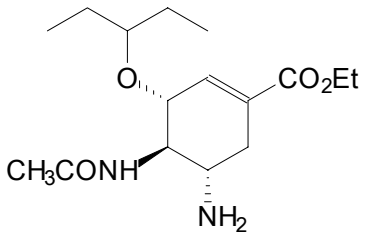
STRENGTHS: 75mg, 45mg, 30mg (as free base); 12mg/mL

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)

SUPPORTING DOCUMENTS: None

REMARKS/COMMENTS:

These "Supplement for Prior Approval" submissions provide for revisions to the labeling to comply with the Physician's Labeling Rule, and to incorporate directions for pharmacy compounding of Tamiflu Suspension from Tamiflu Capsules.

CONCLUSIONS & RECOMMENDATIONS: **APPROVAL**

The proposed labeling, as revised on 22-FEB-2010, is acceptable. Approval is recommended for these supplements.

(see attached electronic signature page)

J. S. Hathaway, Ph.D.
Reviewing Chemist

cc: Orig. NDA 21-087
Orig. NDA 21-246
OND/DAVDP/Division File
OND/DAVDP/ProjMgr/EThompson
ONDQA/DPE/Chem/JSHathaway
ONDQA/DPE/ChemPAL/SDe
ONDQA/DPE/ChemBranchChf/HPatel

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

JOEL S HATHAWAY
02/23/2010

SWAPAN K DE
02/23/2010
Signed for Hasmukh Patel

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021087/S-048

PHARMACOLOGY REVIEW(S)

PHARMACOLOGIST REVIEW OF GLP EIR (CP 7348.808)

Firm Names: WIL Research Laboratories, LLC
Ashland, OH

(b) (4)

Inspection Dates: WIL: 10/26-30/09
(b) (4)

Inspection Highlights

- Accuracy of the method used to measure concentrations of oseltamivir and its metabolite in brain samples in Study WIL 620001 was not demonstrated in that drug recovery from brain tissue was not evaluated. In light of this deficiency, DSI recommends not accepting the reported brain concentration results.
- The effect of hemolysis on the analysis of oseltamivir concentrations in plasma samples was not evaluated.
- The remaining aspects of Study WIL 620001 are acceptable for review.

Background: At the request of the Division of Anti-viral Products (DAVP), the Division of Scientific Investigations (DSI) conducted an audit of the following study:

NDA:	21-087
IND:	53,093
Rev Div.:	Division of Anti-viral Products (DAVP)
Test Article:	Oseltamivir phosphate (Tamiflu®)
Sponsor:	Hoffmann La Roche, Inc.
Study:	WIL 620001, "An Oral (gavage) toxicity study of Tamiflu in juvenile rats"

Tamiflu® has been approved for the treatment and prophylaxis of influenza viral infection in adults and children 1 year and older. The on-going H1N1 flu pandemic necessitated Agency authorization of emergency use of Tamiflu® in children less than 1 year old. On the approved drug label, the use of Tamiflu® is not indicated for children less than 1 year old based on findings from a non-clinical study conducted in 2001. Specifically, deaths in 7 days-old rats possibly resulting from drug accumulation in brain tissue. The sponsor subsequently submitted revised toxicokinetic data based on reported errors in calculated brain concentrations of oseltamivir that were identified after WIL-620001 was conducted in 2007. A revision of the 2001 nonclinical study report no longer shows drug accumulation in brains of 7 days-old rats.

Study WIL-620001 was designed to evaluate the toxicity, toxicokinetics, and potential behavioral effects of oseltamivir in juvenile rats. No effects on brain histology were reported. Furthermore, brain concentrations of oseltamivir in the WIL study were substantially lower than the concentrations originally reported for the 2001 study.

The in-life portion of this study was conducted at WIL Research Laboratories, LLC in Ashland, OH. The inspection at WIL also included a surveillance portion to assess the firm's compliance with 21 CFR part 58 (Good Laboratory Practice for Nonclinical Laboratory Studies). Details and an evaluation of the Surveillance inspection are provided in Attachment 1.

The bioanalytical portion of Study WIL 620001 was conducted at (b) (4) . This is the first GLP inspection by DSI at this facility.

Inspectional findings at WIL Research Laboratories, LLC, Ashland, OH

Following the inspection (October 26-30, 2009) a Form FDA 483 was issued. Our evaluation of the FDA 483 observations that pertain to the aforementioned study and the firm's response dated November 19, 2009 (Attachment 2) follows.

1. The final study report did not include a description of all circumstances that may have affected the quality or integrity of the data.
In study WIL 620001 the study report does not discuss the impact of the use of a non-GLP and non-validated method for analysis of test article concentration in the brain samples. In the same study report, there is no discussion of the impact of moderate to severe hemolysis in about 90% of the plasma samples.

Although the use of a non-validated method was mentioned in the compliance statement of the final study report, the study director failed to critically evaluate the impact of using a method that was not demonstrated to accurately measure oseltamivir concentrations in brain tissue through appropriate pre-study experiments, during sample analysis, or following a post-study feasibility assessment that suggested the reported concentrations were underestimated up to 40% (final report amendment 1). The inspection at (b) (4) confirmed that the method was not properly assessed (see item 4 below). Furthermore, because a significant number of plasma samples were hemolyzed, an experiment should have been conducted to evaluate accuracy of the plasma assay in hemolyzed samples.

The final report was amended after the inspection (amendment issued November 11, 2009) and stated that these significant bioanalytical deficiencies had no impact on study data. The study director states that "after completion of this study, cross-validation studies were conducted at Roche and (b) (4) which compared the (b) (4) method with the validated Roche method. This cross-validation study showed that the two methods produced results which were overall comparable". However, no data for this cross-validation study were provided and a publication referenced in the amendment (Heinig, K. and Bucheli, F., Journal of Chromatography B, 876 (2008) 129-136) has no information of a cross-validation study.

Furthermore, the study director concludes in the final report amendment that hemolysis has no impact on the plasma concentration data. However, the effect of hemolysis was not evaluated and no data was provided to support this conclusion.

2. The final report failed to accurately reflect study conduct. Section 5.5 states that the brain assays for test article were done according to a validated method although Protocol amendment 2 states that the method is not validated.

The final study report amendment issued on November 11, 2009 for Study WIL 620001 corrected the inaccurate statement.

3. The study director failed to issue protocol amendments in a timely manner. Protocol Amendment I for Study WIL 620001 was issued after changes had been implemented.

Study	Change	Amendment	Document implementing change
WIL 620001	Pooling of blood and brain samples from non-sibling PND 7 rats, and other changes	I, dated 5/17/07	Departmental/Study Director Notification 5/3/07

Although it is objectionable that the firm did not issue a protocol amendment in compliance with GLP regulations, the inspection did not find an impact on the study outcome.

(b) (4)

Following the inspection (b) (4), a Form FDA-483 was issued. Our evaluation of the FDA-483 observations and the firm's response dated (b) (4) (Attachment 3), follows.

4. The analytical method ((b) (4) rat brain; Effective: 21 September 2007) entitled "Determination of Ro 64-0796 and Ro 64-0802 in Rat brain tissue by LC-MS-MS" was not a validated method.

The firm failed to demonstrate precision and accuracy of the method used to measure brain concentrations of oseltamivir and its metabolite in Study WIL-620001 in that extraction of drug from brain tissue was not addressed. Specifically, quality control samples (QCs) used for prestudy validation experiments and for in-study sample analysis were prepared in brain supernatant as opposed to brain tissue homogenate. Furthermore, the firm did not evaluate if drug recovery was affected by the different sample conditions, i.e., brain supernatant (QCs) versus brain tissue homogenate (study samples). Thus, the recovery (extraction efficiency) of the drug and its metabolite from brain tissue is unknown and the accuracy of the reported drug concentrations in brain cannot be assured.

In their response, the firm acknowledged the observation and stated that the non-validated method was approved by the study director and was the sponsor's preference. Nonetheless, use of a method that does not reflect the actual conditions of the study samples is not justified.

5. The same integration parameters were not applied to all the calibration standards, quality controls or study samples for assay of RO0640796 or RO0640802 of plasma samples in the analytical runs 1, 2, 3, 4, 5, 7, 10, 11, 12, 13 or 14, and brain samples in the analytical runs 15, 17, 18, 19, 20 or 21.

The integration parameters for RO0640796 or RO0640802 of plasma samples were modified in the runs 1, 2, 3, 4, 5, 7, 10, 11, 12, 13 or 14. Although not applied consistently, DSI found that the modified integration parameters were used to adjust the baseline or select a proper integration for split peaks. Although a few of the quality control samples or calibration standards were subjected to the modified integrations, it did not affect the run acceptability. No significant bias in data reporting was noted for assay of RO0640796 or RO0640802 of plasma samples during the inspection.

The modification of integration parameters for RO0640796 or RO0640802 of brain samples in the runs 15, 17, 18, 19, 20 or 21 was not assessed since the analytical method for the assay of RO0640796 and RO0640802 in rat brain tissue was invalid (see discussion under item 4 above).

The firm responded that they updated the (b) (4) SOP.LAB.02.04 entitled "Integrating, Reintegrating and Reprocessing Chromatographic Data" to require the use consistent integration parameters for each run.

<u>Recommendations</u>:

Following our evaluation of the inspectional findings at WIL and (b) (4) and their responses to the FDA-483 observations, DSI concludes that:

- Accuracy of the bioanalytical method for measuring oseltamivir concentration in brain was not demonstrated in that drug recovery from brain tissue was not addressed. DSI recommends not accepting the data for RO0640796 (oseltamivir) and RO0640802 (metabolite) in rat brain samples in Study WIL 620001 (see discussion under items 1 and 4 above).
- Although a majority of the plasma samples were hemolyzed, the effect of hemolysis on the performance of the plasma assay was not evaluated by the bioanalytical laboratory; data should be provided to address assay accuracy in hemolyzed samples.
- The remaining portions of Study WIL 620001 are acceptable for review.
- Recommended HQ classification:
    - WIL Research Laboratories: Voluntary Action Indicated (VAI)
    - (b) (4) Voluntary Action Indicated (VAI)

_____
Carol M. Rivera-Lopez, Ph.D.
Pharmacologist

_____
Xikui Chen, Ph.D.
Chemist

Acting Team Leader Concurrence:

Concur: _____ Date: _____

Nonconcurrence: _____ Date: _____
(see attached supervisory memorandum)

Date Assigned: 3/20/09 (Surveillance at WIL)
9/15/09 (Directed at WIL and (b) (4)

EI Date: WIL: 10/26-30/09
(b) (4) 11/16-20/09

District Office: WIL: Cincinnati (CIN-DO)
FEI: WIL: 1526213

Investigators: WIL: Steven Kilker, CIN-DO
WIL: Carol M. Rivera-Lopez, Ph.D., CDER-DSI
(b) (4) Xikui Chen, Ph.D., CDER-DSI

Inspection Type: __X__ Routine Surveillance __X__ Directed
FDA-483 Issued: _____ No __X__ Yes (WIL and (b) (4)
Letter Issued: ____ None _____ PI Letter
_____ Untitled Letter

1st Draft Review Completed: 12/30/2009

FACTS: 1000749 (Surveillance portion – WIL)
1097227 (Directed portion – WIL)

Inspection Conclusion (WIL): Voluntary Action Indicated (VAI)
Inspection Conclusion ((b) (4) Voluntary Action Indicated (VAI)
Final HQ Classification (WIL): VAI
Final HQ Classification ((b) (4) VAI

cc:
DSI/CDER DSI PM TRACK
DSI/GLPBB/Salewski/O'Shaughnessy/Rivera-Lopez/Chen
DAVP/Thompson/Yuen/Ghantous
HFR-CE4525/Kilker
Draft: CRL, XC 12/30/09, 1/21/10
Edits: JAO 12/31/09; 1/22/10
DSI File: GLP0727a and GLP0727b
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21087	ORIG-1	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21246	ORIG-1	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML
NDA-21246	SUPPL-34	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML
NDA-21087	SUPPL-48	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES

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/s/

CAROL M RIVERA-LOPEZ
01/28/2010

XIKUI CHEN
01/28/2010

JACQUELINE A O SHAUGHNESSY
01/28/2010

JOSEPH P SALEWSKI
02/03/2010

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-087**
SERIAL NUMBER:	**S-048**
DATE RECEIVED BY CENTER:	**5/29/2009**
PRODUCT:	**Tamiflu®**
INTENDED CLINICAL POPULATION:	**Treatment and prevention of influenza viral infection**
SPONSOR:	**Hoffmann-La Roche Ltd.**
DOCUMENTS REVIEWED:	**Electronic**
REVIEW DIVISION:	**Division of Antiviral Products (HFD-530)**
PHARM/TOX REVIEWER:	**Ita Yuen, PhD**
PHARM/TOX SUPERVISOR:	**Hanan Ghantous, PhD, DABT**
DIVISION DIRECTOR:	**Debra Birnkrant, MD**
PROJECT MANAGER:	**Elizabeth Thompson, MS**
Date of review submission to DARRTS:	**10/26/2009**

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

Not applicable. Tamiflu® has been approved for marketing. The submission contains information used to update label on "PRECAUTIONS: Pediatric Use" and "ANIMAL TOXICOLOGY" sections.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

Sponsor submitted the following revised label text under "PRECAUTIONS: Pediatric Use" and "ANIMAL TOXICOLOGY" sections as follows:

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 ~~uncertainties regarding the rate of development of the human blood-brain barrier and~~ the unknown clinical significance of non-clinical animal toxicology data for human infants (see **ANIMAL TOXICOLOGY**).

ANIMAL TOXICOLOGY

(b) (4)

~~In a 2-week study in unweaned rats, administration of a single dose of 1000 mg/kg oseltamivir phosphate to 7-day-old rats resulted in deaths associated with unusually high exposure to the prodrug. However, at 2000 mg/kg, there were no deaths or other significant effects in 14-day-old unweaned rats. Further follow-up investigations of the unexpected deaths of 7-day-old rats at 1000 mg/kg revealed that the concentrations of the prodrug in the brains were approximately 1500-fold those of the brains of adult rats administered the same oral dose of 1000 mg/kg, and those of the active metabolite were approximately 3-fold higher. Plasma levels of the prodrug were 10-fold higher in 7-dayold rats as compared with adult rats. These observations suggest that~~

~~the levels of oseltamivir in the brains of rats decrease with increasing age and most likely reflect the maturation stage of the blood-brain barrier. No adverse effects occurred at 500 mg/kg/day administered to 7- to 21-day-old rats. At this dosage, the exposure to prodrug was approximately 800-fold the exposure expected in a 1-year-old child.~~

The suggested revision of this section is as follows:

ANIMAL TOXICOLOGY

(b) (4)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Tamiflu® has been approval for the treatment and prophylaxis of influenza viral infection in people 1 year and older. In the label, usage for pediatric patients younger than 1 year old was not advised. The conclusion in the current label was based mainly on the results of a study conducted by (b) (4) which found high amount of oseltamivir (prodrug) as well as oseltamivir carboxylate (metabolite) in the brains of the neonatal rats (7 and 14 day old), especially the 7 day-olds. The AUC value in the brains of 7 day-old rats was found to be close to 200-fold greater than that in the plasma. This result led to the hypothesis of leaky blood-brain barrier in these young rats. The study was reviewed under IND 53,093.268 (DARRTS document # 318).

A later study performed at WIL (study # WIL-62001) with similar design but more closely spaced doses and detailed neurobehavioral monitoring yielded vastly different brain deposition results. Unlike the findings from Sequani report # 100087, brain exposures to prodrug in the 7 day-old rats were not two magnitude of order greater than those in plasma. The ratios of plasma to brain AUCs for the oseltamivir and oseltamivir carcoxylate were similar between 7 day-old and adult rats. The results of this study prompted re-examination of the calculations done for the report # 100087. It was found that brain prodrug concentrations were overestimated 500-fold because of incorrect calculation adjustment to account for dilution. The new toxicokinetic results disproved the 'leaky blood-brain barrier" hypothesis. It also indicated that the

neurological effects seen in both pediatric patients and neonatal rats were unlikely due to high drug concentrations in the brain. The new study and the revised toxicokinetic/brain deposition results of (b) (4) were reviewed under IND 53,093.470 (DARRTS document # 470) and incorporated into the proposed label.

B. Pharmacologic activity

Not applicable.

C. Nonclinical safety issues relevant to clinical use

None.

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/s/

ITA S YUEN
10/26/2009

HANAN N GHANTOUS
10/27/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021087/S-048

MICROBIOLOGY REVIEW(S)

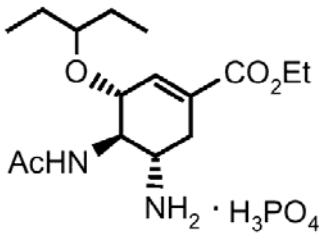
DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW

NDA: 21087 SE-049/21246 SE-035 **SDN** 396 **DATE REVIEWED:** 12/24/09

Reviewer: Damon J. Deming, Ph.D.
Date Submitted: 12/16/09 **Date Assigned:** 12/18/09
Date Received: 12/17/09

Sponsor: Hoffman-LaRoche Inc.
340 Kingsland Street
Nutley, NJ 071101199
Snehal Shah, Pharm.D.
Sr. Program Manager
973-235-5313
973-262-3700 (FAX)

Product Names: Oseltamivir phosphate, Tamiflu
Chemical Names: (3R,4R,5S)-4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester, phosphate
Structure:



OSl

Molecular formula: $C_{16}H_{28}N_2O_4$ (free base)
Molecular weight: 312.4 for the free base, 410.4 for the phosphate salt
Drug category: Antiviral
Indication: (b) (4)

Dosage Form/Route of administration: mg/Oral
Supporting documents: IND 53,093; NDA 21087; NDA 21246
Abbreviations: HAI, hemagglutination inhibition; HSCT, hematopoietic stem cell transplantation; RT-PCR, reverse transcription-polymerase chain reaction; SOT, solid organ transplantation;

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW
NDA: 21087 SE-049/21246 SE-035 **SDN** 396 **DATE REVIEWED:** 12/24/09

BACKGROUND and SUMMARY
This submission consists of the sponsor's reply to a request for more information communicated via FAX on November 5, 2009. The request in presented in bolded text, and the sponsor's reply in italicized text.

Please determine if the H275Y oseltamivir resistance-associated substitution is present in RT-PCR influenza-positive samples, including samples collected at baseline. If the H275Y substitution is not present in isolates from the oseltamivir-treated arm collected during the treatment phase, please extend the sequence analysis to include the entire neuraminidase gene.

Roche proposes to perform H275Y mutation-specific RT-PCR on all available influenza A/H1N1 and influenza A/unknown samples, including both swab sample aliquots and culture supernatants.

For samples found to be negative for the H275Y mutation using the H275Y mutation-specific RT-PCR, Roche proposes to then perform sequence analysis of the neuraminidase gene on all samples for which sufficient material is available (both swab sample aliquots and culture supernatants).

Roche will attempt to generate this data as outlined above, but some testing may not be able to be performed based on the availability of samples.

Roche is seeking FDA's agreement on this proposal before performing the testing. It is estimated that the results can be provided by the end of January 2010 if agreement is reached by the week of January 4, 2010.

COMMENT: Adequate response.

Please identify the clinical study site from which each PT-PCR influenza-positive sample was collected and whether oseltamivir-resistant influenza A (H1N1) was known or suspected to be circulating in that geographic area.

Roche confirmed that of the 24 subjects RT-PCR influenza-positive during treatment, only seven were infected with H1N1 and of these seven, only two were in the active treatment group. All 24 RT-PCR influenza-positive subjects were enrolled in regions with a very low incidence of the resistant strain.

The location of the clinical study site for all RT-PCR influenza positive samples (during treatment, at baseline only, and during follow-up only) is provided in Table 1 below (Appendix). In addition, the incidence of oseltamivir-resistant influenza A (H1N1) is provided for samples that were influenza A/H1N1 or influenza A/unknown subtype.

COMMENT: Adequate response

CONCLUSIONS
We agree with the sponsor's proposed protocol for determining the presence of oseltamivir resistance-associated substitutions within the RT-PCR positive clinical samples of Study NV20235. The incidences of circulating oseltamivir-resistant influenza H1N1 strains were low in the study areas at the time of sample collection.

Damon J. Deming, Ph.D.
Microbiology TL

cc:
HFD-530/IND
HFD-530/Division File
HFD-530/RPM/Thompson

Appendix

Table 1 Subjects with laboratory confirmed influenza by RT-PCR in study NV20235 - geographic region and incidence of H1N1 oseltamivir-resistance

Pt. #	Study Arm	Type	Season[a]	Date of 1st Dose	Geographic Region	Incidence of oseltamivir-resistant influenza A(H1N1)[b]
RT-PCR positive during dosing period						
719	Placebo	A/H1N1	II	29-Jan-08	Jerusalem, Israel	Not available
7203	Placebo	A/H3N2	II	10-Jan-08	Cleveland, OH, USA	n/a
6608	Placebo	A/unk	II	7-Jan-08	Chicago, IL, USA	Low; H3N2 was predominant strain
1514	Placebo	A/H3N2	I	2-Mar-07	Budapest, Hungary	n/a
1544	Placebo	B	II	23-Jan-08	Budapest, Hungary	n/a
1547	Placebo	A/H1N1	II	24-Jan-08	Budapest, Hungary	0
1621	Placebo	A/H1N1	II	24-Jan-08	Szeged (Czongrad), Hungary	0
604	Placebo	A/unk B	II	4-Feb-08	Ramat Gan, Israel	Not available
3808	Placebo	B	II	19-Jan-08	Madrid, Spain	n/a
7602	Placebo	A/H3N2	I	27-Feb-07	Missoula, MT, USA	n/a
802	Placebo	B	I	28-Jan-07	Perach Tikva, Israel	n/a
813	Placebo	B	II	4-Feb-08	Petach Tikva, Israel	n/a
7502	Placebo	A/H1N1	I	16-Feb-07	Newark, DE, USA	0.70%
204	Placebo	B	II	23-Jan-08	Herestraat (Flandre), Belgium	n/a
1324	Placebo	B	II	26-Jan-08	Midi-Pyrenees (Toulouse), France	n/a
6708	Placebo	B	II	18-Jan-08	Denver, CO, USA	n/a
5765	Placebo	A/unk	II	14-Jan-08	Detroit, MI, USA	Low; H3N2 was predominant strain
5778	Placebo	B	II	21-Jan-08	Detroit, MI, USA	n/a
3910	Placebo	B	II	15-Jan-08	Madrid, Spain	n/a
9304	Placebo	B	II	1-Feb-08	Heidelberg, Germany	n/a
716	Oseltamivir	A/H1N1	II	28-Jan-08	Jerusalem, Israel	0
1629	Oseltamivir	B	II	23-Jan-08	Szeged (Czongrad), Hungary	n/a
8604	Oseltamivir	B	I	23-Jan-07	Brooklyn Center, MN, USA	n/a
9305	Oseltamivir	B	II	1-Feb-08	Heidelberg, Germany	n/a
RT-PCR positive at baseline only						
3905	Placebo	A/H1N1	II	15-Jan-08	Madrid, Spain	1.90%
1509	Oseltamivir	A/H1N1	I	28-Feb-07	Budapest, Hungary	Not available
703	Placebo	A/H3N2	I	28-Jan-07	Jerusalem, Israel	n/a
3801	Oseltamivir	A/H3N2	I	15-Feb-07	Madrid, Spain	n/a
6220	Oseltamivir	B	II	31-Jan-08	Birmingham, AL, USA	n/a
601	Oseltamivir	B	II	31-Jan-08	Ramat Gan, Israel	n/a
8603	Placebo	B	I	22-Jan-07	Brooklyn Center, MN, USA	n/a
7102	Placebo	B	I	17-Jan-07	Cincinnati, OH, USA	n/a
RT-PCR positive during follow-up only						
7403	Oseltamivir	B	II	11-Jan-08	Detroit, MI, USA	n/a
6632	Placebo	A/H3N2	II	09-Jan-08	Chicago, IL, USA	n/a

a: Season I = 2006/07, Season II = 2007/08

b: Sources: EuroSurveillance Vol. 13 (July-Sept 2008); ECDC Aug 2008 Antivirals and Antiviral resistance country table: MMWR June 27, 2008/57; MMWR August 10, 2007/56

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21087	SUPPL-48	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES

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/s/

DAMON J DEMING
12/24/2009

JULIAN J O'REAR
12/24/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021087/S-048

OTHER REVIEW(S)

Division of Antiviral Products
Consumer Safety Officer Labeling Review

Application Number: NDA 21-087/S-048 and S-049 and 21-246/S-034 and S-035

Name of Drug: Tamiflu® (oseltamivir phosphate) Capsules and Oral Suspension

Applicant: Hoffman-La Roche, Inc. (Roche)

Submission Date: May 29, 2009 and August 7, 2009

Receipt Date: June 1, 2009 and August 10, 2009

Materials Reviewed:
Previously approved labeling dated September 25, 2008.

Proposed labeling submitted August 7, 2009 and received August 10, 2009 and amended February 22, 2010.

Background and Summary:
On May 29, 2009, Roche submitted a prior approval labeling supplement to convert the package insert for the capsules (NDA 21-087/S-048) and oral suspension (NDA 21-246/S-034) to PLR format. On June 1, 2009, Roche submitted another prior approval labeling supplement to incorporate labeling changes for the capsules (NDA 21-087/S-049) and oral suspension (NDA 21-246/S-035) based on data from the following clinical studies:

- NV20235: "A randomized, controlled, multi-center trial of oseltamivir versus placebo for the seasonal prophylaxis of influenza in immunocompromised patients"

- NV20236: "An open label trial to treat children ages 1-12 for seasonal prophylaxis during influenza season"

The review team decided to review these supplements concurrently and take action on the same date. Comments concerning these supplements were sent to Roche on December 11, 2009, January 5, 2010, January 11, 2010, January 25, 2010, January 29, 2010, February 3, 2010, and February 18, 2010. The final version of the label was submitted on February 22, 2010. The first time PLR conversion was reviewed by the SEALD team and comments were relayed to the sponsor.

Review:

1. The Highlights of Prescribing Information was updated to reflect changes throughout the label.

2. The following statement was added at the first point under Section 1.3 **Limitations of Use**:

- Efficacy of TAMIFLU in patients who begin treatment after 48 hours of symptoms has not been established.

3. The following statement was moved from the fourth point to the third point under Section 1.3 **Limitations of Use**:

- There is no evidence for efficacy of TAMIFLU in any illness caused by agents other than influenza viruses Types A and B.

4. Throughout the label, [redacted] (b) (4) was changed to [redacted] (b) (4)

5. Throughout the label, [redacted] (b) (4) was changed to [redacted] (b) (4)

6. The last two columns in Tables 1 and 2 were renamed as follows:

   Number of Bottles of TAMIFLU for Oral Suspension [redacted] (b) (4) to Dispense [redacted] (b) (4) for a 5-Day Regimen

   Number of TAMIFLU Capsules [redacted] (b) (4) to Dispense [redacted] (b) (4) for a 5-Day Regimen

7. The first paragraph under Section 2.3 **Standard Prophylaxis of Influenza** now reads:

   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. Safety has been demonstrated for up to 12 weeks in immunocompromised patients. The duration of protection lasts for as long as dosing is continued.

8. The last paragraph under Section 2.3 **Standard Prophylaxis of Influenza** now reads:

   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.

9. The [redacted] was removed from the end of Section 2.3 **Standard Prophylaxis of Influenza**.

10. Section 2.4 [redacted] was renamed to **Renal Impairment**.

11. The [redacted] statement was removed from the beginning of Section 2.4 **Special Dosage Instructions**.

12. The first paragraph under Section 2.4 **Renal Impairment** now states:

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

13. The *Treatment of Influenza* part of Section 2.4 **Renal Impairment** now reads:

    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 [redacted] continuous peritoneal dialysis treatment [redacted]

14. The *Prophylaxis of Influenza* part of Section 2.4 **Renal Impairment** now reads:

    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.

15. **Hepatic Impairment** was added as Section 2.5 and **Geriatric Patients** was added as Section 2.6. All subsequent sections were renumbered accordingly.

16. Section 2.5 **Hepatic Impairment** now states:

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

17. The [redacted] statement under section 2.7 **Preparation of TAMIFLU for Oral Suspension** was deleted [redacted]

18. The last paragraph of Section 2.7 **Preparation of TAMIFLU for Oral Suspension** now reads:

    The constituted TAMIFLU for oral suspension [redacted](12 mg/mL) should be used within 17 [redacted] 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.

19. Table 3 under Section 2.8 **Emergency Compounding of an Oral Suspension from TAMIFLU Capsules (Final Concentration 15 mg/mL)** now states:

Body Weight (kg)	**Body Weight (lbs)**	**Total Volume to Compound per Patient [redacted] (mL)**
≤15 kg	≤33 lbs	30 mL
>15 [redacted] to 23 kg	>33 [redacted] to 51 lbs	40 mL
>23 [redacted] to 40 kg	>51 [redacted] to 88 lbs	50 mL
>40 [redacted] kg	>88 [redacted] lbs	60 mL

20. The compounding procedure under Section 2.8 **Emergency Compounding of an Oral Suspension from TAMIFLU Capsules (Final Concentration 15 mg/mL)** was changed as follows:

- Determine the number of capsules and the amount of vehicle (Cherry Syrup or Ora-Sweet SF) that are needed to prepare the total volume.
- Carefully separate the capsule body and cap and transfer the contents of the required number of TAMIFLU 75 mg capsules [redacted] into a clean mortar.
- Triturate the granules to a fine powder.
- Slowly add a small amount of vehicle (approximately 1 mL per 6 capsule contents) to the triturated TAMIFLU powder and levigate well with the pestle (approximately 2-3 minutes) to a smooth mass. Continue adding very slowly the remainder of [redacted]-one-third (1/3) of the total [redacted]-amount of vehicle in 3 small portions to [redacted]-the mortar while triturating with the pestle [redacted] until a uniform suspension is achieved each time.
- Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
- Add the second [redacted]-one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar by a triturating motion, and transfer the vehicle into the bottle.
- Repeat the rinsing with the remaining one-third (1/3) [redacted]-of the vehicle.
- Close the bottle using a child-resistant cap.

- Shake well 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 [redacted] (b) (4) -inert ingredients of TAMIFLU capsules [redacted] (b) (4) -which are insoluble in these vehicles.)
- Put an ancillary label on the bottle indicating "Shake Gently Before Use." (Note: This compounded suspension should be gently shaken prior to administration to minimize the tendency for air entrapment, particularly with the Ora-Sweet SF preparation.)
- Instruct the parent or caregiver [redacted] (b) (4) -that any unused suspension remaining in the bottle [redacted] (b) (4) -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.
- Place an appropriate expiration date on the label according to storage conditions [redacted] (b) (4) -below.

21. Under Section 2.8 **Emergency Compounding of an Oral Suspension from TAMIFLU Capsules (Final Concentration 15 mg/mL)** STORAGE OF THE PHARMACY COMPOUNDED SUSPENSION was replaced with Storage of the Compounded Suspension.

22. A Dosing of the Compounded Suspension (15 mg/mL) clarifier was added Under Section 2.8 **Emergency Compounding of an Oral Suspension from TAMIFLU Capsules (Final Concentration 15 mg/mL)**.

23. The weight ranges in Table 5 Under Section 2.8 **Emergency Compounding of an Oral Suspension from TAMIFLU Capsules (Final Concentration 15 mg/mL)** were changed in accordance with the changes in Table 4.

24. Section 3 **DOSAGE FORMS AND STRENGTHS** now states:

- 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: 12 mg/mL (final concentration)

- White powder blend for constitution to a white tutti-frutti–flavored suspension. Each bottle delivers 25 mL of suspension equivalent to 300 mg oseltamivir base.

25. Section 4 **CONTRAINDICATIONS** now reads:

    TAMIFLU is contraindicated in patients with known serious hypersensitivity to oseltamivir or any component (b) (4) 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)]*.

26. The second paragraph under Section 5.2 **Neuropsychiatric Events** now states:

    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 (b) (4) with influenza (b) (4) for signs of abnormal behavior. If neuropsychiatric symptoms occur, evaluate the risks and benefits of continuing treatment (b) (4) for each patient.

27. Section 5.3 **Limitations of Populations Studied** was moved after the **Bacterial Infections** section and appropriately renumbered.

28. Section 5.3 **Limitations of Populations Studied** now reads:

    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.

29. Section 6 ADVERSE REACTIONS now states:

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.

30. The term "(b) (4) was changed to "(b) (4) throughout the label.

31. Column titles in table 6 and table 7 under Section 6.1 **Clinical Trials Experience** were updated to clarify the terms bid (changes to twice daily) and qd (changed to once daily). Oseltamivir was changed to Tamiflu. The following footnote was added to both tables to further describe an adverse event:

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

32. The last paragraph in the *Treatment Studies in Pediatric Subjects* subsection was revised as follows:

    Adverse events occurring in ≥1% of pediatric subjects receiving TAMIFLU treatment are listed in Table 7. 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 (b) (4) discontinuation of drug in 8 out of 515 (1.6%) (b) (4)

33. The following age-based table was removed and appropriate wording was added to the clarifying statement after Table 6 under Section 6.1 **Clinical Trials Experience**:

    (b) (4)

    The statement now reads: [d] Unit dose = age-based dosing of 30 mg, 45 mg, or 60 mg

34. Under Section 7 **DRUG INTERACTIONS**, the information presented was divided into two subheadings which included *Influenza Vaccines* and *Overall Drug Interaction Profile for Oseltamivir*.

35. Warfarin was added to the list of drugs exhibiting no interactions with oseltamivir under Section 7 **DRUG INTERACTIONS**.

36. The first paragraph in Section 8.4 **Pediatric Use** now states:

    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 (b) (4) –the unknown clinical significance of non-clinical animal toxicology data for human infants *[see Nonclinical Toxicology (13.2)]*.

37. Section 8.6 is now titled **Renal Impairment** and Section 8.7 was changed to **Hepatic Impairment**.

38. Section 8.6 **Renal Impairment** now reads:

    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.

39. Section 8.7 **Hepatic Impairment** now states:

    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 (2.4) and Clinical Pharmacology (12.3)]*.

40. Section 12.1 **Mechanism of Action** was changed to the following:

    (b) (4)

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

41. Table 8 under Section 12.3 **Pharmacokinetics** was renamed **Mean (% CV) Pharmacokinetic Parameters of Oseltamivir and Oseltamivir Carboxylate Following** (b) (4) **-Multiple Dosing of 75 mg Capsules Twice Daily-** (b) (4) **(n=20)**

42. Column titles in table 9 under Section 12.3 **Pharmacokinetics** were updated to clarify the terms bid (changes to twice daily) and qd (changed to once daily).

43. A Mechanism of Action subsection was added to Section 12.4 **Microbiology**:

    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.

44. The last paragraph of Section 12.4 **Microbiology** now states:

    In clinical studies of postexposure and seasonal prophylaxis in immunocompetent subjects, determination of resistance by population nucleotide sequence analysis was limited by the low overall incidence rate of influenza infection and prophylactic effect of TAMIFLU. (b) (4)

45. Section 13.2 **Animal Toxicology and/or Pharmacology** was replaced with the following paragraph:

    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 (AUC0-24h) of oseltamivir and oseltamivir carboxylate, respectively. Clinical relevance of the juvenile rat study finding for young infants is unknown.

46. Section 14.1 was renamed from (b) (4) to **Treatment of Influenza**.

47. Section 14.2 was renamed from (b) (4) to **Prophylaxis of Influenza**.

48. The Immunocompromised Subjects subsection of Section 14.2 **Prophylaxis of Influenza** was revised as follows:

    A double-blind, placebo controlled study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised subjects (b) (4) (including 18 pediatric subjects (b) (4) -1 - 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 (b) (4) –for this study was the incidence of (b) (4) 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 [redacted]-or a four-fold increase in virus antibody titers from baseline. The [redacted]–incidence of [redacted]–confirmed clinical influenza was [redacted]–3% (7/238) in the group not receiving TAMIFLU compared with [redacted]–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. [redacted]

—Among subjects who were not already shedding virus at baseline, [redacted]–the incidence of RT-PCR [redacted]-confirmed clinical influenza was [redacted]–3% (7/231) in the group not receiving TAMIFLU and [redacted]-<1% (1/232) in the group receiving TAMIFLU. [redacted]

49. The last paragraph of the *Storage* subsection of Section 16 **HOW SUPPLIED/STORAGE AND HANDLING** now states:

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

50. Section 17 **PATIENT COUNSELING INFORMATION** refers the reader to *See FDA-approved Patient Labeling*.

51. The following two paragraphs were added to the beginning of Section 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.

52. Under Section 17.1 **Information for Patients**, the phrase [redacted] was changed to "Instruct patients."

53. The revision date was updated at the end of the labeling.

Conclusions:

These prior approval labeling supplements are acceptable based on review team revisions requested by the Division and an approval letter should be sent to the sponsor.

_____
Robert G. Kosko, Jr., Pharm.D., M.P.H.
Regulatory Project Manager

_____
Vicky Tyson
Chief, Project Management

23 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21246	SUPPL-34	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML
NDA-21087	SUPPL-48	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21087	SUPPL-49	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21246	SUPPL-35	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML

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/s/

Robert G Kosko
02/22/2010

VICTORIA L TYSON
02/22/2010

DSI CONSULT: Request for Non-Clinical Inspections

Date: July 13, 2009

To: C.T. Viswanathan, Ph.D., Associate Director
Division of Scientific Investigations
Office of Compliance/CDER

Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Ita Yuen, Ph.D., Nonclinical Reviewer, DAVP
Hanan Ghantous, Ph.D., Nonclinical TL, DAVP

From: Elizabeth Thompson, Regulatory Project Manager, DAVP

Subject: **Request for High Priority Non-Clinical Site Inspection**

I. General Information

Application#: NDA 21-087

Applicant/ Applicant contact information (to include phone/email):

Hoffmann-La Roche, Inc.
Attention: S. Elizabeth Lucini, Pharm.D.
Program Manager
Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

(973) 235-6141
elizabeth.lucini@roche.com

Drug Name: Tamiflu

Proposed Indication(s): Treatment of influenza

II. Study Identification

Study title: RO0640796 (oseltamivir phosphate; Tamiflu™): Pharmacokinetics of the prodrug, oseltamivir, and active metabolite in the plasma and brains, and toxicity after a single oral administration of the prodrug to juvenile rats ((b) (4) , Roche Study No. 7021K07)

Laboratory Contact	Study Number	Study Description	Indication
(b) (4)		Nonclinical study in juvenile rats	Influenza viral infection

III. Site Selection Rationale

Tamiflu® has been approved for the treatment and prophylaxis of influenza viral infection in adults and children 1 year and older. The on-going H1N1 flu pandemic necessitated the authorization of emergency use of Tamiflu® in children less than 1 year old by the Agency. On the approved drug label, the use of Tamiflu® is not indicated for children less than 1 year old based on findings from a nonclinical study; specifically, deaths in 7 day-old rats. Those deaths were thought to be the result of drug accumulation in brain tissue, an apparent effect of the immature blood brain barrier. Recently a revision to that nonclinical study report was submitted to the Agency. The revised toxicokinetic data no longer shows drug accumulation in brains of the 7 day-old rats. The decision to override the Agency's earlier health concerns for children less than 1 year old was based in part on the revised toxicokinetic data in 7 day-old rats. DAVP is requesting that DSI inspect the GLP study records against the original and revised report to verify the accuracy of the revised pharmacokinetic data. Thus, a high priority should be placed on the requested DSI non-clinical inspection.

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
___ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
_____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

(b) (4)

Should you require any additional information, please contact *Elizabeth Thompson, RPM* at *301-796-0824 or Ita Yuen* at *301-796-0838.*

Concurrence: (as needed)

_____HG 7-14-09_____Pharm/Tox Supervisor
_____IY 7-14-09_____ Pharm/Tox Reviewer
____DB 7-14-09_____ Division Director

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/s/

Elizabeth Thompson
7/15/2009 09:54:18 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021087/S-048

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-087/S-048 and S-049
NDA 21-246/S-034 and S-035

GENERAL ADVICE

Hoffmann-La Roche Inc.
Attention: Sukirti D. Mukheja, B.S., Pharm.D.
Senior Program Manager
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Mukheja:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAMIFLU (oseltamivir phosphate) 30 mg, 45 mg and 75 mg capsules and 12 mg/mL oral suspension.

We also refer to the February 23, 2010 approval letter for supplements 048 and 049 for NDA 21-087 and 034 and 035 for NDA 21-246 to convert the Package Insert (PI) to PLR format and incorporate labeling changes based on data from studies NV20235 and NV20236. The carton and container labeling and the Patient Package Insert (PPI) were not attached to the approval letter. We have attached the approved carton and container labeling and PPI to this letter.

If you have any questions, call Robert G. Kosko, Jr., Regulatory Project Manager, at (301) 796-3979 or at the Division's main number (301) 796-1500.

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

13 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21246	SUPPL-34	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML
NDA-21087	SUPPL-48	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21087	SUPPL-49	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21246	SUPPL-35	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML

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/s/

JEFFREY S MURRAY
02/23/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: February 18, 2010

To: S. Elizabeth Lucini, Pharm.D. Program Manager, Drug Regulatory Affairs	**From:** Robert G. Kosko, Jr., Pharm.D., M.P.H. Regulatory Project Manager
Company: Hoffman-La Roche, Inc.	Division of Antiviral Products
Fax number: (973) 235-6141	**Fax number:** (301)796-9883
Phone number: (973) 562-3700	**Phone number:** (301)796-3979

Subject: NDA 21-087/S-049 and 21-246/S-035: Comments for Tamiflu Efficacy Supplement

Total no. of pages including cover: 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-087/S-049 and 21-246/S-035

Drug: Tamiflu (oseltamivir phosphate) Capsules and Oral Suspension

Date: February 18, 2010

Sponsor: Hoffmann-La Roche, Inc.

From: Robert G. Kosko, Jr., Pharm.D., M.P.H., Regulatory Project Manager

To: S. Elizabeth Lucini, Pharm.D., Program Manager, Drug Regulatory Affairs

Subject: Comments for Tamiflu Efficacy Supplement

A Microsoft Word version of the following label with the review team's suggested revisions and comments was sent to the sponsor via email on February 18, 2010.

Robert G. Kosko, Jr., Pharm.D., M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

26 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21246	SUPPL-34	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML
NDA-21087	SUPPL-48	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21087	SUPPL-49	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21246	SUPPL-35	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML

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/s/

Robert G Kosko
02/19/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products

FACSIMILE TRANSMITTAL SHEET

DATE: February 3, 2010

To: Sukirti D. Mukheja, BS, Pharm.D. Pharma Development Regulatory	**From:** Robert G. Kosko, Jr., Pharm.D., M.P.H. Regulatory Project Manager
Company: Hoffman-La Roche, Inc.	Division of Antiviral Products
Fax number: (973) 562-3720	**Fax number:** (301)796-9883
Phone number: (973) 562-3700	**Phone number:** (301)796-3979

Subject: NDA 21-087/S-048 and NDA 21-246/S-034: Comment for 1-18-10 Submission

Total no. of pages including cover: 4

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-087/S-048 and 21-246/S-034

Drug: Tamiflu (oseltamivir phosphate)

Date: February 3, 2010

Sponsor: Hoffmann-La Roche, Inc.

From: Robert G. Kosko, Jr., Pharm.D., M.P.H., Regulatory Project Manager

To: Sukirti D. Mukheja, BS, Pharm.D., Pharma Development Regulatory

Subject: Comment for 1-18-10 Submission

Please refer to your submission dated January 18, 2010. We are proposing the following wording for the label under "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_{0-24h}) of oseltamivir and oseltamivir carboxylate, respectively. Clinical relevance for young infants is unknown.

Labeling Comments:

1. Since the main point of this section is a description of the juvenile animal findings, the lead sentence should begin with that point, not that there was no toxicity in adult rats.

2. The safety margins of 280- and 14-fold were calculated based on the human AUC values of 224 and 5428 ng-hr/ml.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE**. Please feel free to contact me at 301-796-3979 if you have any questions regarding the contents of this transmission.

Robert G. Kosko, Jr., Pharm.D., M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21087	SUPPL-48	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21246	SUPPL-34	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML

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/s/

Robert G Kosko
02/03/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products
Division of Antiviral Products

FACSIMILE TRANSMITTAL SHEET

DATE: January 11, 2010

To: S. Elizabeth Lucini, Pharm.D. Program Manager, Drug Regulatory Affairs	**From:** Robert G. Kosko, Jr., Pharm.D., M.P.H. Regulatory Project Manager
Company: Hoffman-La Roche, Inc.	Division of Antiviral Products
Fax number: (973) 235-6141	**Fax number:** (301)796-9883
Phone number: (973) 562-3700	**Phone number:** (301)796-3979

Subject: NDA 21-087/S-048 and 21-246/S-034: Comments for Tamiflu PLR Conversion (Revised Section 13.2)

Total no. of pages including cover: 3

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-087/S-048 and 21-246/S-034

Drug: Tamiflu (oseltamivir phosphate) Capsules and Oral Suspension

Date: January 11, 2010

Sponsor: Hoffmann-La Roche, Inc.

From: Robert G. Kosko, Jr., Pharm.D., M.P.H., Regulatory Project Manager

To: S. Elizabeth Lucini, Pharm.D., Program Manager, Drug Regulatory Affairs

Subject: Comments for Tamiflu PLR Conversion (Revised Section 13.2)

A Microsoft Word version of the following label revision for section 13.2 was sent to the sponsor via email on January 11, 2010:

(b) (4)

[redacted]

Robert G. Kosko, Jr., Pharm.D., M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21246	SUPPL-34	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML
NDA-21087	SUPPL-48	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES

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/s/

Robert G Kosko
01/12/2010

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: January 5, 2010

To: S. Elizabeth Lucini, Pharm.D. Program Manager, Drug Regulatory Affairs	**From:** Robert G. kosko, Jr., Pharm.D., M.P.H. Regulatory Project Manager
Company: Hoffman-La Roche, Inc.	Division of Antiviral Products
Fax number: (973) 235-6141	**Fax number:** (301)796-9883
Phone number: (973) 562-3700	**Phone number:** (301)796-3979

Subject: NDA 21-087/S-048 and 21-246/S-034: Comments for Tamiflu PLR Conversion

Total no. of pages including cover: 21

~~DEPARTMENT OF HEALTH & HUMAN SERVICES~~ ~~Public Health Service~~

Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-087/S-048 and 21-246/S-034

Drug: Tamiflu (oseltamivir phosphate) Capsules and Oral Suspension

Date: January 5, 2010

Sponsor: Hoffmann-La Roche, Inc.

From: Robert G. Kosko, Jr., Pharm.D., M.P.H., Regulatory Project Manager

To: S. Elizabeth Lucini, Pharm.D., Program Manager, Drug Regulatory Affairs

Subject: Comments for Tamiflu PLR Conversion

A Microsoft Word version of the following label with the review team's suggested revisions and comments was sent to the sponsor via email on January 5, 2010.

Robert G. Kosko, Jr., Pharm.D., M.P.H.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

19 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21087	SUPPL-48	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES
NDA-21246	SUPPL-34	HOFFMANN LA ROCHE INC	TAMIFLU (OSELTAMIVIR PHOSPHATE) 12MG/ML

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/s/

Robert G Kosko
01/06/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-087/S-048
NDA 21-246/S-034

PRIOR APPROVAL SUPPLEMENT

Hoffmann-La Roche Inc.
Attention: S. Elizabeth Lucini, Pharm.D.
Program Manager
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Dr. Lucini:

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Products: TAMIFLU (oseltamivir phosphate) capsules
TAMIFLU (oseltamivir phosphate) oral suspension

NDA/Supplement Numbers: 21-087/S-048
21-246/S-034

These supplemental applications propose the following changes:

1. Content and format of labeling provided in PLR

2. Package Insert

   - DOSAGE AND ADMINISTRATION/Preparation of TAMIFLU for Oral Suspension: revised to reflect proposed update to storage conditions

   - NONCLINICAL TOXICOLOGY/Animal Toxicology and/or Pharmacology: revised to reflect analysis of preclinical data from juvenile rat studies

   - HOW SUPPLIED/TAMIFLU for Oral Suspension: revised to reflect proposed update to storage conditions/stability of Tamiflu for Oral Suspension

3. Patient Package Insert

   - How and where should I store TAMIFLU?: revised to reflect proposed update to storage conditions

4. Carton/Container label

- Revision proposed to the 12/mg/mL oral suspension carton/container label reflecting update to storage conditions.

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 July 31, 2009, in accordance with 21 CFR 314.101(a).

Please 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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Elizabeth Thompson
6/10/2009 07:31:14 AM