

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021087/S-049

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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
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**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
NDA 021087/S-049

APPROVAL LETTER



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(1)(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
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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

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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 $\geq 1\%$ 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

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

^a Adverse events included are all events reported in the treatment studies with frequency $\geq 1\%$ 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

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

^a Adverse events included in Table 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)*].

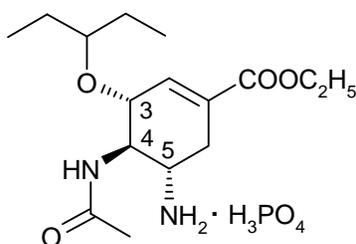
10 OVERDOSAGE

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 _{0-12h} (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 (EC₅₀ and EC₉₀) 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_{0-24h}) of oseltamivir carboxylate.

13.2 Animal Toxicology and/or Pharmacology

Single, oral administration of ≥ 657 mg/kg oseltamivir resulted in toxicity, including death, in juvenile 7 day old rats, but had no effect on adult rats. No toxicity was observed after repeated administration of up to 500 mg/kg oseltamivir to developing juvenile rats 7 to 21 days old. This 500 mg/kg dose was approximately 280 and 14

times the human systemic exposure (AUC_{0-24h}) 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 >100°F, 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 (>100°F) 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 $\geq 99.0^{\circ}\text{F}/37.2^{\circ}\text{C}$ 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 $\geq 100^{\circ}\text{F}/37.8^{\circ}\text{C}$ 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 $> 99.0^{\circ}\text{F}/37.2^{\circ}\text{C}$ 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 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [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 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

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].

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.

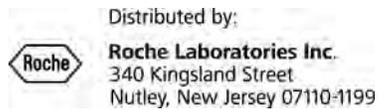
Instruct patients to begin treatment with TAMIFLU as soon as possible from the first appearance of flu symptoms. Similarly, prevention should begin as soon as possible after exposure, at the recommendation of a physician.

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.

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Rev. February 2010

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021087/S-049

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. [REDACTED] (b) (4)
Recommended:	<i>Approval, with modifications in proposed labeling as noted</i>

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 ≥ 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 ≥ 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 $> 37.2^{\circ}\text{C}$ 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 ≥ 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.

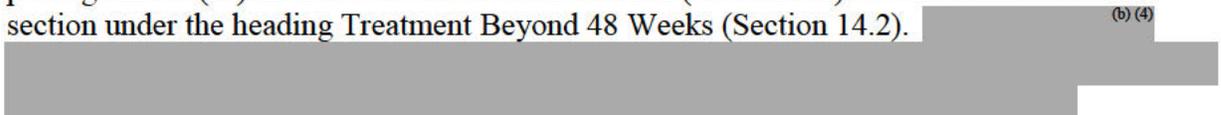
The current supplement does not trigger additional pediatric PMCs under the provisions of the Pediatric Research Equity Act (PREA).

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. [REDACTED] (b) (4)

[REDACTED] However, 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-049

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type sNDA
Application Number(s) 21-087/S-049, 21-246/S-017
Priority or Standard P

Submit Date(s) 08-10-2009
Received Date(s) 08-10-2009
PDUFA Goal Date 02-10-2010
Division / Office DAVP/OAP

Reviewer Name(s) Tafadzwa Vargas-Kasambira,
M.D., M.P.H.
Review Completion Date January 29, 2010

Established Name Oseltamivir phosphate
(Proposed) Trade Name Tamiflu®
Therapeutic Class Antiviral
Applicant Hoffman-La Roche Inc.

Formulation(s) Dry Powder for Oral
Suspension or 75 mg Capsule
Dosing Regimen Weight dependent once daily
dosing

Indication(s) Treatment and Prophylaxis of
Influenza

Intended Population(s) Immunocompromised subjects

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Clinical Review
{Tafadzwa Vargas-Kasambira, MD, MPH}
{NDA 21-087/S-049, 21-246/S-017}
{Tamiflu® (oseltamivir phosphate)}

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The element of the Post Marketing Commitment (PMC) to evaluate Tamiflu as prophylaxis in immunocompromised patients has been fulfilled with the completion of study NV20235. The Food and Drug Administration (FDA) has incorporated the results of this study in immunocompromised subjects in the product label. The study did not meet its primary efficacy endpoint, and therefore conclusions regarding the efficacy of 12 weeks of oseltamivir (Tamiflu) use in immunocompromised subjects for prevention of influenza infection, cannot be fully substantiated. However, a key secondary efficacy analysis supports use of Tamiflu in this population. Safety data for the 12 week duration of therapy in this population were obtained.

The applicant proposes oseltamivir for daily use in adult and pediatric hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients for a duration of 12 weeks during the influenza season. The approved capsules and oral suspension formulations (in children aged 1 to 12 years) were used in the study. The primary efficacy endpoint (incidence of laboratory-confirmed clinical influenza as assessed on treatment, defined by fever $> 37.2^{\circ}\text{C}$, and symptoms of cough and/or coryza in the same 24 hour period, with laboratory confirmation by either viral culture or four-fold increase in serum hemagglutination inhibition assay (HAI)) was not met in this study. The incidence of confirmed clinical influenza was 2.9% (7/238) in the placebo group, and was 2.1% (5/237) in the oseltamivir group, a difference that was not significant ($p=0.27$). Secondary endpoints were explored based on the primary endpoint analysis, using various combinations of laboratory confirmation methods (serology, viral culture, and RT-PCR). When RT-PCR was used as the method of laboratory confirmation, 7 placebo subjects (3%) and 1 oseltamivir subjects ($<1\%$) were found to have the diagnosis of influenza.

No deaths occurred during 12-week period of subject participation and follow-up in the study, but there were two subjects who died after being withdrawn from the study. Both of these deaths were in the placebo group; there were no deaths in the oseltamivir group. A total of 82 non-fatal serious adverse events (SAEs) were reported in the study, with 49 SAEs occurring in the placebo group, and 33 SAEs occurring in the oseltamivir group. The most frequent SAEs were in the infections and infestations class (placebo 12/237 or 5%; oseltamivir 10/238 or 4%). No new oseltamivir-related SAE signals were identified in the study population. Fifty-one subjects (11%) withdrew from the study prematurely, with 33 subjects in the placebo group and 18 subjects in the oseltamivir group. This total included 14 subjects (6%) from the placebo group and 7 subjects (3%) from the oseltamivir group who were withdrawn for reasons of safety.

The most frequently reported AEs that led to withdrawal from the study were gastrointestinal in the placebo group (two AEs of diarrhea, one of dyspnea, one of gastrointestinal hemorrhage, accounting for 2% of AEs), and gastrointestinal (dyspnea in < 1% of AEs) and nervous system disorders (one AE of cerebrovascular accident, one of anxiety, and one of amnesia, accounting for 1% of AEs) in the oseltamivir group.

Eight placebo subjects and seven oseltamivir subjects had their study medication dosing frequency changed from daily to every other day due to creatinine clearance levels of ≤ 30 mL/min. The most commonly reported AEs for subjects while “on treatment”, in both groups. Were gastrointestinal disorders (placebo 22%, oseltamivir 21%), followed by infections and infestations (placebo 19%, oseltamivir 18%). The majority of AEs that occurred were of mild severity. The AEs noted in this study were similar in nature and in frequency to rates of AEs in previous prophylaxis and treatment studies using Tamiflu.

1.2 Risk Benefit Assessment

Tamiflu was approved for use in the United States on October 27, 1999. Post marketing events have been reported, and include dermatologic, digestive, cardiac, gastrointestinal, neurologic, metabolic, and psychiatric symptoms and disorders. Nervous system disorders were evaluated in the study, and none of the AEs in this class (e.g. amnesia) were AEs that have been reported as psychiatric AEs in post marketing use of Tamiflu.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) will not be required for this study.

1.4 Recommendations for Postmarket Requirements and Commitments

The applicant has fulfilled the prophylaxis part of the PMC through completion of this study under review, and study NV20236, an open-label, multi-center study of oseltamivir for seasonal prophylaxis of influenza in children. Study NV20236 was reviewed by Dr. Julie-Ann Crewalk (see section 5.3 for summary of the study). The second part of this PMC, to evaluate Tamiflu in the treatment of influenza in immunocompromised patients, is in progress as study NV20234.

2 Introduction and Regulatory Background

Clinical Review

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{NDA 21-087/S-049, 21-246/S-017}

{Tamiflu® (oseltamivir phosphate)}

2.1 Product Information

- **Name:** Oseltamivir phosphate (Tamiflu®)
- **Description:** Dry powder reconstituted to a concentration of 12 mg/mL, and 75 mg capsules
- **Chemical Class:** (3R,4R,5S) -4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester phosphate (1:1)
- **Chemical Formula:** C₁₆H₂₈N₂O₄ (free base)
- **Pharmacological Class:** Selective inhibitor of influenza A and B neuraminidases

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2.2 Tables of Currently Available Treatments for Proposed Indications

The current indications are for the treatment and prophylaxis of influenza. The currently approved drugs for these indications are described specifically in the following table:

Table 1. Currently Available Treatments for Treatment and Prophylaxis of Influenza

Available Treatment	Indication
Tamiflu (oseltamivir phosphate)	Treatment (5 days) of uncomplicated acute illness due to influenza infection in adults, adolescents and children 1 year and older who have been symptomatic for no more than 2 days
Tamiflu	Prophylaxis of influenza in adults and adolescents for up to 6 weeks, during community outbreaks
Tamiflu	Prophylaxis of influenza in patients 1 year or older after known exposure (10 days)
Relenza (zanamivir)	Treatment of uncomplicated acute illness due to influenza A or B in adults and children 7 years and older who have been symptomatic for no more than 2 days
Relenza	Prophylaxis of influenza in adults and children 5 years and older
Symmetrel (amantadine hydrochloride)	Treatment and prophylaxis of signs and symptoms of infection caused by various strains of influenza A virus

Available Treatment	Indication
Flumadine (rimantadine hydrochloride)	Treatment and prophylaxis of illness caused by various strains of influenza A in adults
Flumadine	Prophylaxis against influenza A in children

2.3 Availability of Proposed Active Ingredient in the United States

Oseltamivir phosphate, the active ingredient in Tamiflu, is available in the United States by prescription only.

2.4 Important Safety Issues with Consideration to Related Drugs

Not applicable.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Interactions for study NV20235 – Seasonal prophylaxis in immunocompromised patients

Nov 17, 2000 – Oseltamivir was approved for prophylaxis of influenza for adults and adolescents 13 years and older. The PMC instructed the company to investigate the safety and effectiveness of oseltamivir for treatment and prevention of influenza infection in immunocompromised patients.

May 18, 2006 – A Special Protocol Assessment (SPA) request submitted by Roche for Protocol NV20235 as they wanted to use data from the study to fulfill the PMC, and update safety and efficacy data in label. Final comments were provided to Roche on September 25, 2006.

Nov 8, 2006 – Roche submitted a protocol amendment NV20235B

August 7, 2009 – Roche submitted the final CSR for NV20235

Interactions for study NV20236 – Seasonal prophylaxis in pediatric patients

Dec 21, 2005 – Oseltamivir was approved for prophylaxis of influenza following known exposure in children 1 to 12 years of age. The PMC instructed Roche to collect safety data in a population of 40 to 50 pediatric patients 1 to 12 years of age using approved prophylaxis dosing recommendations for up to 6 weeks in the setting of seasonal influenza prophylaxis. Evaluation of “influenza high risk” patient groups was suggested by DAVP.

May 18, 2006 – An SPA request was submitted for Protocol NV20236 as Roche wanted to use data from the study to fulfill the PMC, and update safety and efficacy data in label.

June 9, 2006 – The study did not qualify for SPA as it did not fit the criteria required.

Nov 8, 2006 – Roche submitted a protocol amendment NV20236B

May 6, 2008 – Roche submitted the final CSR for NV20236

June 19, 2009 – FDA concluded that the PMC from the sNDA approved December 21, 2005 was fulfilled based on this study.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The applicant submitted the sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate.

3.2 Compliance with Good Clinical Practices

According to the applicant, this study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments, or with the laws of the country in which the research was conducted, whichever afforded greater protection to the individual. The study was also said to have adhered fully to the principles outlined in “*Guidance for Good Clinical Practice*” International Conference on harmonization Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the subject. The applicant also states that investigators ensured adherence to the EU Clinical Trial Directive (2001/20/EC) and to the basic principles of Good Clinical Practice as outlines in the current version of 21CFR, subchapter D, part 312, “*Responsibilities of Sponsors and Investigators*”, part 50, “*Protection of Human Subjects*”, and part 56, “*Institutional Review Boards*” (IRB).

3.3 Financial Disclosures

The sponsor submitted financial information pertinent to the application. The Disclosure: Financial interests and Arrangements of Clinical investigators was signed on May 22, 2009 by the sponsor, stating that sub-investigator (b) (6) received honoraria and grants towards the Department of Nephrology at the (b) (6) in excess of \$25,000. The sponsor does not believe that these payments influenced in any way the results reported by (b) (6) or influenced the overall outcome of the study as the results from this center were consistent with those from other study centers, and for the trial outcome overall.

On May 22, 2009 the sponsor signed the same Disclosure with reference to the remainder of investigators who participated in the study, stating that they had not entered into any financial arrangement with these clinical investigators whereby the value of the payment could affect the outcome of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Tamiflu is an FDA-approved drug, and CMC did not, therefore, review this sNDA submission.

4.2 Clinical Microbiology

Please refer to the Microbiology/Virology review for this sNDA.

4.3 Preclinical Pharmacology/Toxicology

Tamiflu is an FDA-approved drug, and Pharmacology/Toxicology did not, therefore, review this submission. Pharmacology/Toxicology did, however, review the new labeling for accuracy of the data and conclusions included.

4.4 Clinical Pharmacology

Tamiflu is an FDA-approved drug, and Clinical Pharmacology did not, therefore, review this submission. In addition, no new clinical pharmacology studies were submitted for review by this team.

4.4.1 Mechanism of Action

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

4.4.2 Pharmacodynamics

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate, and is converted extensively by hepatic esterases (among other enzymes) to oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure after oral dosing. The volume of distribution of oseltamivir carboxylate, following intravenous administration in 24 subjects, ranged from 23 to 26 liters. Protein binding is low (3%). Neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome P450 isoforms. Absorbed oseltamivir is primarily eliminated by conversion to oseltamivir carboxylate (> 90%). The half-life of oseltamivir is approximately 1 to 3 hours in most subjects (6 to 10 hours for oseltamivir carboxylate). Oseltamivir carboxylate is not further metabolized and is eliminated in the urine. Less than 20% of an oral radiolabeled dose is eliminated in feces.

4.4.3 Pharmacokinetics

Oseltamivir carboxylate comprises approximately 75% of any oral dose that reaches the systemic circulation. Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily. Coadministration with food has no effect on the peak plasma concentration and the area under the plasma concentration time curve of oseltamivir carboxylate.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The efficacy results from four other studies were previously submitted in May 2000 in support of the approved prophylaxis indication. These are outlined in the following table

Table 2. Table of Previous Tamiflu Studies

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{Tamiflu® (oseltamivir phosphate)}

. Study Number	Design	Phase	Objective	Results
WV15825	Multicenter, randomized, double-blind, placebo-controlled studies	2	Prospectively evaluate efficacy of oseltamivir in seasonal prevention of laboratory-confirmed clinical influenza in immunocompetent elderly (≥ 65 years) occupants of residential homes following 6 weeks of dosing	Tamiflu 75 mg once a day for 42 days reduced the incidence of lab-confirmed influenza from 4.4% for the placebo group to 0.4% for the Tamiflu group.
WV15673 and WV15697	Identical randomized, double-blind, placebo-controlled studies	3	Prospectively evaluate efficacy of oseltamivir in the seasonal prevention of laboratory-confirmed clinical influenza in healthy adults following 6 weeks of dosing (data pooled from both studies for analysis)	Tamiflu 75 mg once a day for 42 days reduced the incidence of lab-confirmed influenza from 4.8% for the placebo group, to 1.2% for the Tamiflu group.
WV15799	Cluster-randomized, double-blind, placebo-controlled, parallel group study	3	Investigate efficacy of oseltamivir in prevention of laboratory-confirmed clinical influenza post-exposure in immunocompetent subjects aged ≥ 13 years exposed to a case of clinical influenza within the same living environment.	Tamiflu 75 mg once a day administered within 2 days of exposure to index case and continued for 7 days reduced the incidence of lab-confirmed influenza from 12% in the placebo group to 1% in the Tamiflu group. Index cases did not receive Tamiflu.
WV15708	Double-blind, randomized, placebo-controlled, parallel-group study	3	Prospectively evaluate the efficacy of oseltamivir in the prevention of laboratory-confirmed clinical influenza in immunocompetent elderly (≥ 65 years of age) occupants of residential homes (safety data pooled with studies WV15825 and studies WV15763/WV15697)	See results for Study WV15825.

5.2 Review Strategy

The clinical information provided by the applicant for this study was reviewed. The materials that were submitted included the NV20235 Clinical Study Report (CSR) and Data Sets for study NV20235. Case Report Forms (CRFs) for all patients who died within 28 days of the last treatment dose, for all patients who withdrew from the studies due to related or unrelated adverse events, and for all patients who experienced SAEs during study drug dosing, were included. In addition, narratives were provided for all subjects who experienced deaths, SAEs (drug-related and non drug-related), and all drug-related AEs leading to withdrawal.

5.3 Discussion of Individual Studies/Clinical Trials

The submission contains clinical summaries of two separate studies: NV20235 and NV20236

NDA 21-246/S-031 is summarized in this MO review. Study NV20236, submitted in response to a PMC, was reviewed by Julie-Ann Crewalk, M.D. on June 11, 2009. The findings will be summarized in this section (please see full review for further details).

Summary of Clinical Review of Study NV20236

The review of this study report was based upon an open-label, multi-center trial of oseltamivir for seasonal prophylaxis of influenza in children. It was submitted on May 6, 2008 to fulfill the Postmarketing Commitment included in the December 21, 2005 FDA Approval Letter for sNDAs 21-246/S-017 and NDA 21-087/S-030. The letter requested safety data for the use of Tamiflu in a population of 40 to 50 “high risk” patients aged 1 to 12 years. The currently approved prophylaxis dosing recommendations for post-exposure prophylaxis with Tamiflu were to be used for 6 weeks in the setting of seasonal influenza prophylaxis.

The final study report was amended on May 28, 2008 to provide a correction of the summary of the disposition of patients. This amendment did not change the overall conclusions made previously by the reviewing Medical Officer.

Brief Overview of Clinical Program

Study NV20236 was an open-label, multi-center trial of oseltamivir for the seasonal prophylaxis of influenza in children. Tamiflu is approved for the treatment and prophylaxis of influenza in patients 1 year of age and older. Prophylaxis has been evaluated for up to 6 weeks in adults and adolescents, and for 10 days in children older than 1 year of age. Prophylaxis in children for greater than 10 days has not been

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previously evaluated. The current recommended dosing for prophylaxis in children is: 30, 45, 60, or 75 mg, dependent on pediatric weight, orally each day for 10 days. The purpose of this study was to assess safety and tolerability of oseltamivir as prophylaxis for influenza in high risk children aged 1 to 12 years for up to 6 weeks.

A total of 52 subjects between the ages of 1 and 12 years were enrolled. Subjects received one dose of oral oseltamivir (Tamiflu) daily for 6 weeks.

Efficacy

This open-label study was focused primarily on safety and tolerability, so no major efficacy conclusions can be made. Certain efficacy endpoints were noted, however, at the end of the study, and these are summarized below:

- There were no noted cases of laboratory-confirmed clinical influenza (defined as a positive viral culture or a > 4 fold increase in antibody titer, along with fever, cough and coryza, or by fever and cough or coryza)
- Three subjects developed laboratory-confirmed clinical influenza, as noted by a ≥ 4 fold increase in antibody titer at the follow-up visit
- Two subjects who experienced influenza symptoms, had increased antibody titers, but did not meet the criteria for clinical influenza
- Three subjects developed symptoms of clinical influenza, but did not have any supportive laboratory evidence to confirm this diagnosis

Safety

A total of 49 subjects were included in the safety profile as 3 subjects did not return post-baseline for assessment. Forty-one subjects completed treatment. Thirty-two of the 49 subjects (65%) received more than 100% of the expected cumulative dose (i.e. more than 84 doses total for the duration of the study), with 43 of the 49 subjects (88%) receiving 29 to 42 doses.

Significant findings in the safety assessment included the following:

- There were no deaths or serious adverse events (SAEs) noted in the study
- Two subjects were withdrawn from the study due to adverse events (AEs). One of the subjects was a 3 year old male with oral blistering that was noted on day 4 of treatment. The second subject was an 11 year old female with a 10-day history of nausea. The nausea was considered by the investigator to be possibly related to treatment.
- During the “On Treatment” period, 17 of the 49 subjects (35%) reported a total of 22 AEs
- The most common “On Treatment” AEs included: gastrointestinal (n=6), and infections and infestations (n=6). Twelve AEs were of mild intensity, and 8 AEs

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were of moderate intensity. There were two severe AEs noted: toothache and otitis media

- Three AEs (mild nausea, moderate nausea, and emesis) were considered to be possibly related to treatment
- The most common “Off Treatment” AEs included: infection (n=3), joint injury (n=1), headache (n=1), and wheezing (n=1). None of these reported AEs were considered to be related to treatment
- Three subjects received more than the prescribed dose, and one of these subjects experienced multiple AEs, including ear pain and tendonitis during treatment, and otitis media and sinusitis during follow-up. This subject’s AEs were all considered to be unrelated to the treatment
- No dose modifications were made for safety reasons. One subject had treatment withheld for 3 days due to a diagnosis of acute otitis media. This subject did resume and complete treatment
- Four episodes of marked laboratory abnormalities were noted in the last assessment of the trial, and none were replicated (per the applicant). These abnormalities included: eosinophilia in two subjects (both had a history of asthma and/or hypersensitivity); low neutrophil count in one subject; and elevated AST and ALT in a fourth subject. None of these laboratory abnormalities were reported as AEs
- There were no clinically significant changes from baseline in vital signs or laboratory values (any abnormalities in either were also seen at baseline)

Drug-Drug Interactions

Although information derived from pharmacology and PK studies of oseltamivir suggests that clinical significant drug interactions are unlikely, the potential for antiviral drugs to inhibit live vaccine virus replication still exists. Therefore, subjects with a recent history (2 weeks prior to enrollment) of live influenza vaccine administration (FluMist®) were excluded from the study.

Assessment and Conclusions

All 52 subjects received at least one dose of oseltamivir, and a total of 49 subjects were included in the safety profile (3 did not return post-baseline for assessment). Forty-one subjects (78.8%) completed treatment, while 7 received treatment for influenza-like symptoms and 2 subjects received treatment for other medical reasons.

There were no cases of laboratory-confirmed clinical influenza. Ten subjects underwent influenza testing post-baseline. Three subjects had ≥ 4 fold increase in influenza antibody titer at the end of treatment assessment, while another 3 subjects had influenza confirmed by a similar increase in titer at the follow-up visit.

No deaths were noted, and there were no SAEs reported. Two subjects were withdrawn from the study due to adverse events that included oral mucosal blistering and nausea. Consent was withdrawn by 4 subjects (75% stated that the taste of the medication was the reason), and 2 other subjects refused treatment. The most common AEs were gastrointestinal disturbances (nausea, vomiting), and infections (nasopharyngitis, tonsillitis, sinusitis, and otitis media).

Symptoms consistent with influenza illness such as headache, cough, sore throat, and myalgias, were not included as AEs. This approach may have potentially led to a decreased incidence of true AEs being reported. While there did not appear to be an increase in AEs due to the increased duration of the medication, adherence may prove difficult in younger children due to the prolonged course of therapy and the taste of the medication.

Conclusion

There were no new safety signals identified in children using oseltamivir, and the submitted Phase 4 Commitment study has shown that prophylaxis with oseltamivir for 6 weeks is generally safe and well-tolerated in children. Given the fact that this is a small, open-label study, conclusions regarding efficacy of long term use for the prevention of influenza cannot be drawn.

Recommendation on Regulatory Action

It was recommended that the applicant submit new labeling for Tamiflu based on the submitted PMC study. Labeling recommendations have been included in this supplement.

6 Review of Efficacy

Efficacy Summary of Study NV20235

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6.1.1 Methods

This trial was a prospective, parallel group, randomized, double-blind, multicenter study of oseltamivir versus placebo for the seasonal prophylaxis of influenza in immunocompromised subjects as represented by solid organ transplant (SOT) [liver,

kidney, or liver and kidney], or hematopoietic stem cell transplant (HSCT) recipients. Only subjects who were relatively stable and whose short-term prognosis was good were enrolled. Subjects included in the study had undergone SOT or HSCT, were age 1 year or older, negative for an influenza rapid diagnostic test, and had no influenza-like illness symptoms at enrollment.

Randomization was stratified by transplant type (SOT or HSCT), influenza vaccination status (yes or no), and age (<13 years or ≥ 13 years). The protocol planned for enrollment of 470 subjects (235 in each group) who met inclusion criteria, at 44 different centers across the United States and Europe. Subjects received prophylaxis treatment for 12 weeks (84 days) when surveillance data indicated that influenza was active in the community. A follow-up visit was conducted 28 days after the conclusion of prophylaxis. Subjects were encouraged to make unscheduled visits to the study clinic at any time during treatment whenever they had influenza symptoms. At these illness visits, vital signs and nasal and throat swabs were collected for detection of influenza virus by RT-PCR and viral culture. Influenza vaccination in the last 4 weeks prior to randomization led to exclusion from the study.

General Discussion of Endpoints

The efficacy endpoints in the study included the following:

Primary Efficacy Endpoint: The incidence of laboratory-confirmed clinical influenza (“standard” definition) as assessed on treatment defined as:

1. Fever (oral or otic temperature > 37.2°C; and
2. Symptom score of 1, 2, or 3 for cough and/or coryza (nasal congestion on the diary cards) on the same day from the fourth day of study drug dosing until the end of the treatment period; and
3. Laboratory confirmation of influenza by either of the following
 - Detection of viral shedding by viral culture from nasopharyngeal swabs within 2 days of fever or cough and/or coryza and measured from study day 4 up to 2 days after the last dose of test medication
 - Four-fold or greater increase in serum HAI titers measured at baseline from study day -30 to study day 1 and post baseline from study day 2 up to 35 days after the last dose of test medication

Secondary Efficacy Endpoints:

1. Laboratory-confirmed clinical influenza using the following definitions of laboratory confirmation for influenza virus:
 - a. Positive viral culture, 4-fold or greater increase in HAI titers, or positive RT-PCR (“all” definition of laboratory confirmation)
 - b. Positive RT-PCR (“RT-PCR definition for laboratory confirmation)
2. Infection with fever (oral or otic temperature > 37.2°C) using the standard, all, and RT-PCR definitions for laboratory confirmation

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3. Infections with symptoms (cough/coryza) using the standard, all, and RT-PCR definitions for laboratory confirmation
4. Laboratory-confirmed asymptomatic influenza defined as absence of a fever (oral or otic temperature $\leq 37.2^{\circ}\text{C}$), cough, and coryza (symptom score < 1) using the standard, all, and RT-PCR definitions for laboratory confirmation
5. Influenza-like illness not caused by the influenza virus on the same day without detection of virus shedding using the standard, all, and RT-PCR definitions for laboratory confirmation
6. Fever without laboratory confirmation of influenza
7. Symptoms without laboratory confirmation of influenza

Additionally, the incidence of secondary illnesses (bronchitis, pneumonia, sinusitis, and otitis media) in subjects with laboratory-confirmed clinical influenza was to be analyzed.

Exploratory endpoints included the following:

- Incidence of the illness categories clinical case; febrile URTI; URTI with systemic disturbance; URTI without systemic disturbance; febrile constitutional; asymptomatic with no fever; asymptomatic with fever; and asymptomatic with no fever and ≥ 1 constitutional symptom (endpoints previously used in studies of oseltamivir in healthy adults)
- Clinical course of influenza in subjects who develop influenza
- Incidence of rejection and graft-versus-host-disease
- Predictive value of serology for RT-PCR

All screening assessments were made within 24 hours of first dose. Efficacy parameters included temperature and the symptoms for influenza-like illness, and these were captured on the diary card. Influenza symptoms were recorded using a nominal scale from zero (absent/no problem) to three (severe or major problem) with a score of zero being considered asymptomatic. Vital signs and influenza symptoms were recorded at scheduled study visits. Efficacy laboratory parameters included blood draws for hematology, chemistry, and serology assessments at selected visits, as well as nasal and throat swabs at each scheduled visit for detection of influenza virus shedding by RT-PCR and viral culture. HAI titers were considered diagnostic of influenza as part of the “all” definition, as previously mentioned, if there was a 4-fold increase from baseline.

Analysis Populations

Four populations were used for the analysis of data from this study:

1. *Intent-to-treat (ITT) Population*: All subjects randomized to receive at least one dose of test drug medication and who had at least one post baseline efficacy assessment. This was the primary analysis population for efficacy endpoints.

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2. *Intent-to-treat Virus Negative at Baseline (ITTNAV) Population*: Subset of the ITT population who were influenza negative at baseline. This population excluded all subjects who had laboratory confirmed influenza by RT-PCR or viral culture at baseline.

3. *Per Protocol Population*: Subset of the ITT population who did not have any major protocol violations which would impact the assessment of efficacy. Major violations included: subjects who did not fulfill inclusion or exclusion criteria; laboratory-confirmed influenza by RT-PCR and/or viral culture at baseline; compliance with study medication < 80%; vaccination during the study; concomitant use of intravenous immunoglobulin; received test drug medication other than that to which randomized; no post-baseline efficacy assessments

4. *Safety Population*: Included all subjects who received at least one dose of study medication and had a post-baseline safety assessment.

On or Off Trial Treatment Definitions

The protective benefit from oseltamivir is achieved only during treatment due to the short half-life of the drug. Therefore fever or cough/coryza were considered “on treatment” if they occurred during treatment (excluding the first 3 days of continuous study medication intake), and laboratory confirmation of influenza by RT-PCR or viral culture was considered on treatment if the swab was taken up to 2 days after the last dose of study medication. A 4-fold change in HAI titer up to 35 days after last dose of test medication was considered on treatment.

Fever or cough/coryza that occurred after the last dose of study medication was considered “off treatment.” Laboratory confirmation by RT-PCR or viral culture was considered off treatment if the swab was taken more than 2 days after the last dose of study medication.

Medical Officer’s comments: Although the protocol stratifies by influenza vaccination status, there is no attention given to the differences in HAI titer amongst subjects of different ages and immune states in this stratification scheme. One of the two definitions for laboratory-confirmed influenza included a positive viral culture, 4-fold or greater increase in HAI titers, or positive RT-PCR (“all” definition). Certain studies have shown that the period of peak HAI titers to an influenza vaccine extends in the elderly, from 1 to 2 weeks in younger individuals, to 6 weeks in the elderly¹, and that post-vaccination titers of HAI are lower than those among younger individuals². Depending upon at what time

1 Gross PA, Russo C, Dran S, Cataruozolo P, Munk G, Lancey SC. Time to earliest peak serum antibody response to influenza vaccine in the elderly. Clin Diagn Lab Immunol. 1997;4(4):491-2

2 Hara M, Tanaka K, Hirota Y. Immune response to influenza vaccine in healthy adults and the elderly: association with nutritional status. Vaccine 2005;23(12):1457-63

influenza is acquired, the HAI titer may not meet the “all” definition of laboratory confirmation within the 12 week study period in some elderly patients.

Studies have shown that antibody response following vaccination is often lower in transplant recipients. The response of renal recipients to booster doses of pneumococcal vaccine, and tetanus and diphtheria toxoids appears to be adequate but reduced in comparison to that in immunocompetent persons³. In response to influenza vaccination, the seroconversion rates of transplant recipients are also generally less than in control populations⁴. Influenza immunization of HSCT recipients less than six months following transplantation is not likely to produce protective antibody titers, and is not recommended. The issues concerning less reliable antibody titers in response to influenza vaccination are generally less significant > 24 months following transplantation, depending on the patient’s level of immunosuppression⁵.

6.1.2 Demographics

The main demographics characteristics of the study population are shown in the table below:

3 Huzley D, Neifer S, Reinke P, et al. Routine immunization in adult renal transplant recipients. *Transplantation* 1997;63:839

4 Blumberg EA, Albano C, Pruett T, et al. The immunogenicity of influenza virus vaccine in solid organ transplant recipients. *Clin Infect Dis* 1996;22:295

5 *MMWR Recommendations and Reports*, "[Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients: Recommendations of CDC, the Infectious Diseases Society of America, and the American Society of Blood and Marrow Transplantation](#)". Oct 20, 2000/49(RR10);1-128

Table 3. Demographics of Study Population (Safety Population) - Age

	Placebo N= 237	Oseltamivir N = 238	Placebo N = 237	Oseltamivir N = 238	Placebo N = 237	Oseltamivir N = 238	Placebo N = 237	Oseltamivir N = 238
Age Category (years)	1 – 10		11 – 20		21 – 30		31 - 40	
n	7	9	8	6	13	8	36	31
Mean	5	5.7	16.0	15.2	26.7	25.8	35.9	36.4
SD	3.27	3.39	2.83	2.86	2.06	2.44	2.79	2.54
Min-Max	1-10	1-10	12-20	11-19	22-29	21-28	31-40	31-40

	Placebo N= 237	Oseltamivir N = 238	Placebo N = 237	Oseltamivir N = 238	Placebo N = 237	Oseltamivir N = 238	Placebo N = 237	Oseltamivir N = 238
Age Category (years)	41 – 50		51 – 60		61 – 70		> 71	
n	45	60	60	71	53	40	9	13
Mean	45.6	45.7	56	56.1	64.5	65.2	73.7	72.6
SD	2.93	2.95	2.66	2.75	2.79	2.49	0.5	1.76
Min-Max	41-50	41-50	51-60	51-60	61-70	61-70	73-74	71-76

Medical Officer’s comment: The largest cohort of subjects was aged 51 to 60 years. There were relatively few children and adolescents (< 21 years of age) enrolled in the study.

Table 4. Demographics of Study Population (Safety Population)

	Placebo N = 237	Oseltamivir N = 238
Sex		
Female	86 (36%)	74 (31%)
Male	151 (64%)	164 (69%)
n	237	238
Race		
Asian	3 (1%)	1 (<1%)
Black	15 (6%)	20 (8%)
White	219 (92%)	215 (90%)
Other	-	2 (<1%)
n	237	238
Ethnicity		
Hispanic	8 (3%)	3 (1%)
Non-Hispanic	229 (97%)	235 (99%)
n	237	238
Weight (kilograms)		
Mean	76.4	76.4
SD	20.36	21.27
Median	75.0	76.4
Min-Max	10.0 – 133.5	9.0 – 144.0
n	236	237
Height (cm)		
Mean	167.8	168.7
SD	14.57	16.07
Median	170.0	170.0
Min-Max	76 – 192	79 – 197
n	234	235

n represents number of subjects contributing to summary statistics (differences represent missing data).

Percentages are based on n (number of valid responses)

*Two subjects (87506/0720 and 87588/7117) in oseltamivir group excluded from ITT population due to lack of efficacy data

Medical Officer’s comment: There was a higher number of males and whites enrolled in the study than females or other races. This difference was consistent in both treatment groups. Height and weight differences were similar between the groups as well.

Table 5. Study Center Information

Country	Number of Centers N = 148
USA	68
Poland	12
Canada	10
Germany	10
France	7
Israel	6
Great Britain	6
Belgium	6
Italy	5
Estonia	4
Hungary	4
Czech Republic	3
Lithuania	3
Spain	2
The Netherlands	2

Medical Officer's comment: The majority of study centers were located in the United States (46%), with the remainder in European countries.

Table 6. Summary of Transplant History and Influenza Status at Baseline

	Placebo N = 237	Oseltamivir N = 238
Type of Transplant		
HSCT	43 (18%)	44 (18%)
Kidney	149 (63%)	156 (66%)
Liver	42 (18%)	36 (15%)
Kidney and Liver	3 (1%)	2 (<1%)
n	237	238
Time since HSCT Transplant (days)		
Mean	889.3	626.9
SD	871.13	867.04
Median	424.0	367.0
Min-Max	49 - 3204	40 - 5486
n	43	44
Time since SOT Transplant (days)		
Mean	1834.4	1932.4

	Placebo N = 237	Oseltamivir N = 238
SD	1847.46	1728.18
Median	1110.0	1371.5
Min-Max	110 - 10011	188 - 9589
n	193	190
Influenza vaccination status*		
Yes	98 (41%)	93 (39%)
No	139 (59%)	145 (61%)
n	237	238
Time since vaccination (days)		
Mean	85.7	87.1
SD	26.09	22.55
Median	91.0	88.0
Min-Max	6 - 135	36 - 136
n	63	66
Rapid diagnostic test for influenza		
Negative	237 (100%)	238 (100%)
Positive	-	-
n	237	238
RT-PCR (irrespective of influenza type)		
Missing	3 (1%)	-
Negative	227 (96%)	233 (98%)
Positive	7 (3%)	5 (2%)
n	237	238
Viral culture§		
Missing	232 (98%)	233 (98%)
Negative	4 (2%)	4 (2%)
Positive	1 (<1%)	1 (<1%)
n	237	238
Creatinine clearance category¶		
10 to < 30	8 (4%)	5 (2%)
≥ 30	213 (96%)	220 (98%)
n	221	225

The majority of subjects had received solid organ transplants, with most receiving kidney transplants (63%). There was no significant difference between the two treatment arms in terms of type of transplant received. There did appear to be a significant difference between the two treatment groups in terms of the time from HSCT; the mean time from transplantation for the placebo group was approximately 2.5 years, while that for the oseltamivir group was approximately 1.5 years. The difference was not as pronounced between the treatment groups in subjects who had received SOT (approximately 5 years in both groups). More subjects in both treatment groups were not vaccinated against influenza at the time of enrollment in the study (59% in placebo

group, 61% in oseltamivir group). The mean time since influenza vaccination was approximately 12 weeks in both groups. As noted in the table, there was no significant difference between the treatment groups in terms of rapid diagnostics testing for influenza, RT-PCR, viral culture, or creatinine clearance category.

Medical Officer’s comment: The fact that there was a difference between the type of transplantation received may be significant in the outcome of the trial, although this difference was balanced between the two treatment arms. The level and complexity of immunosuppression for SOT recipients may be different from that of HSCT recipients. In addition, the fact that the subjects in the oseltamivir group underwent their HSCT more recently than those in the placebo group may place those in the HSCT group (who, in addition, did not receive prophylaxis against influenza) at greater risk of infection.

In addition, the data on criteria for transplantation are not provided by the applicant, but it is likely that these criteria differ in the study sites in the United States and in Europe, as does the post-transplantation management. The latter involves the practice of supplying immunosuppressive agents, which may be supplied for varying periods of time based on local standards and practices. Should immunosuppressive agents be administered at significantly different rates at different sites, susceptibility to influenza infection will likely vary.

Most subjects in the study had not been vaccinated against influenza at the time of enrollment. The influenza infection rates were low in this study, in both treatment arms, despite these low vaccination rates. For those who were vaccinated at the time of enrollment, the time to vaccination was approximately 12 weeks in both groups, which should be enough time (even in those who are immunosuppressed) to mount an immune response.

Exclusions from Analysis Populations

The table below shows the exclusions from each of the study populations, and the reasons why these subjects were excluded.

Table 7. Exclusions from Analysis Populations

First Trial Medication	Placebo N = 237	Oseltamivir N = 238
Exclusion From Analysis Population		
ITT	-	2 (<1%)
ITTNAB	7 (3%)	7 (3%)
Per protocol	32 (%)	20 (%)
Safety	-	2 (<1%)

No other protocol violation n'	8 (%) 45	6 (%) 36
Reason for Exclusion, By Study Population		
Excluded from ITT Population	-	2 (<1%)
No efficacy information	-	2 (<1%)
Excluded from ITTNAB Population	7 (3%)	7 (3%)
Laboratory-confirmed influenza at baseline	7 (3%)	5 (2%)
No efficacy information	-	2 (<1%)
Excluded from Per Protocol Population	32 (14%)	20 (8%)
Compliance < 80%	14 (6%)	7 (3%)
Concomitant IV immunoglobulin	6 (3%)	5 (2%)
Laboratory-confirmed influenza at baseline	7 (3%)	5 (2%)
Incorrect test medication	1 (<1%)	-
Influenza-like illness at baseline	3 (1%)	1 (<1%)
Influenza vaccination in prior 4 weeks	1 (<1%)	-
No efficacy information	-	2 (<1%)
Excluded from Safety Population	-	2 (<1%)
No safety information	-	2 (<1%)
Excluded from No Other Protocol Violation		
Completed incorrect diary for age	-	1 (<1%)
Test medication administered BID	1 (<1%)	1 (<1%)
Dose other than prescribed	4 (2%)	2 (<1%)
Incorrectly stratified – vaccination status	4 (2%)	2 (<1%)
Incorrectly stratified – transplant type	-	1 (<1%)

The most common reasons for exclusion overall were compliance < 80% and laboratory-confirmed influenza at baseline (6% each category) in the placebo group, and laboratory-confirmed influenza (4%) in the oseltamivir group.

Medical Officer’s comment: Some of the applicant’s reasons for exclusion from the analysis may not be relevant for the purposes of the FDA review. It is not clear that an error in stratification for transplant type or vaccination status, for example, would affect the efficacy results significantly, due to the fact that the affected number of subjects is small. These subjects were not excluded from the FDA efficacy analysis.

6.1.3 Subject Disposition

A total of 477 subjects (238 placebo, 239 oseltamivir) were randomized in the study. A higher percentage of subjects in the oseltamivir group (92%) completed the study compared with subjects in the placebo group (85%). This trend held regardless of whether the reasons were safety-related (placebo 6%; oseltamivir 3%) or non-safety-related (placebo 9%; oseltamivir 5%).

The reasons most frequently reported for subject withdrawal were adverse events (AEs) – of which there were twice as many in the placebo group (6%) compared with the oseltamivir group (3%) – and refusal of treatment (placebo 4%; oseltamivir 3%). No subjects were prematurely withdrawn from the study because of death.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint in this study was the incidence of laboratory-confirmed clinical influenza as assessed on treatment. Laboratory-confirmed clinical influenza on treatment was defined as a fever (oral or otic temperature > 37.2°C) and a symptom score of 1, 2, or 3 for cough and/or coryza (nasal congestion on the diary cards) on the same day, from the fourth day of study drug dosing until the end of the treatment period, and laboratory confirmation by either of the following:

- Detection of viral shedding by viral culture from nasopharyngeal swabs within 2 days of fever or cough and/or coryza and measured from study day 4 up to 2 days after the last dose of test medication
- Four-fold or greater increase in serum HAI titers measured at baseline from study day =30 to study day 1 and post baseline from study day 2 up to 35 days after the last dose of test medication.

This definition of laboratory confirmation is referred to throughout the study as the “standard” definition for laboratory confirmation of influenza.

Results

The applicant found that seven placebo subjects (2.9%) and five oseltamivir subjects (2.1%) met the criteria for laboratory confirmed (by serology and/or viral culture) clinical influenza on treatment (the p-value of this difference was not significant, with 95% confidence interval -2.3% to 4.1%, p=0.772). The relative reduction in the risk for developing laboratory-confirmed clinical influenza (i.e. treatment effect) in subjects who received oseltamivir prophylaxis was found by the applicant to be 28.3%. Therefore, in the ITT population, oseltamivir was not shown to be superior to placebo for preventing the incidence of standard laboratory-confirmed clinical influenza.

Clinical Review

{Tafadzwa Vargas-Kasambira, MD, MPH}

{NDA 21-087/S-049, NDA 21-246/S-017}

{Tamiflu® (oseltamivir phosphate)}

The applicant performed the Cochran-Mantel-Haenszel test as a supporting analysis of the primary endpoint, stratifying by transplant type, influenza vaccination status, and age. This analysis confirmed the results of the primary analysis ($p=0.56$). The applicant also found that positive viral culture was reported for more placebo subjects ($n=4$) than oseltamivir subjects ($n=1$).

The applicant provided possible explanations for the failure to meet the primary endpoint in this study. The study was designed to demonstrate 80% protective efficacy (with 80% power and a two-sided 0.05 level test), assuming an attack rate of 7.0% in the placebo group, and 1.4% in the oseltamivir group, using a sample size of 470 subjects ($n=235$ per treatment group). Due to the fact that the overall attack rates observed in the study (i.e. primary endpoint for placebo 2.9%, and for oseltamivir 2.1%) were lower than expected, the primary endpoint was not met. The applicant states that a larger sample size would have been needed to demonstrate a statistically significant treatment effect for the analysis of the primary endpoint.

Another explanation the applicant suggested for the failure to meet the primary endpoint involved the immune function of the study subjects. The applicant claims that in an immunocompromised patient population, diagnostic assessments of influenza infection based on immune function (i.e. serology) may not be as predictive as direct measures of influenza virus (viral culture and RT-PCR). Although a large portion of subjects met the definition of having laboratory-confirmed influenza based upon a serological response, the applicant believes that this may have represented a non-specific immune response to vaccination, or other unknown factors related to immune dysfunction. The applicant also indicates that various clinical symptoms such as fever, which, though nonspecific, was required to meet the clinical case definition, may have been confounded by the immunosuppression in this population that was predisposed to infection.

Medical Officer's comment: The applicant's first explanation for the failure to meet the primary endpoint appears to be logical. Low influenza attack rates would necessitate a higher number of susceptible subjects in order to increase the likelihood of noting a difference between the placebo and oseltamivir treatment groups. The applicant's suggestion that serology may be a nonspecific or unreliable predictor of immune response in immunocompromised subjects does not take into account the level of immunosuppression, or the immune status of the subjects at the time of the study.

The mean time since HSCT in both treatment groups was more than 1.5 years, and the mean time since SOT in both groups was above 5 years. Given the fact that immune function in transplant recipients who are not significantly immunosuppressed is generally regarded as being close to normal 24 months after transplantation (see MO comments in section 6.1.1), the applicant's rationale

is problematic. One would have expected an adequate serological response to influenza infection in the majority of study subjects.

It should be noted that the primary endpoint was sought in the ITT population, and not in the ITTNAB population, although even in the latter, the applicant did not find a significant difference between the treatment groups (laboratory-confirmed influenza in placebo group 7 (3.0%) versus 4 (1.7%), 95% CI -1.7% to 4.6%, $p=0.381$). The ITTNAB population was assessed for the secondary endpoints.

Please refer to the Statistical Review of this study for further explanation.

6.1.5 Analysis of Secondary Endpoints(s)

According to the applicant, secondary endpoint analyses were carried out based on the primary endpoint analysis using various combinations of laboratory confirmation methods such as serology, viral culture, and RT-PCR, in the various analysis populations (ITT, ITTNAB, and per protocol) and illness categories (e.g. infection with fever, infection with symptoms, asymptomatic). No sensitivity analyses or robustness checks were conducted by the applicant for the secondary endpoints. A summary of the secondary endpoints is shown in the table below, by treatment group:

Table 8. Summary of ITTNAB Subjects with Laboratory-confirmed Clinical Influenza Infection*

Laboratory Protocol	Placebo N=231	Oseltamivir N=232
“Standard” definition	7 (3%)	4 (2%)
“All” definition	8 (4%)	4 (2%)
“RT-PCR” definition	7 (3%)	1 (<1%)

*Laboratory confirmation: Fever ($>37.2^{\circ}\text{C}$), symptoms (cough and coryza) and confirmation by viral culture, seroconversion, or RT-PCR

Standard definition: Lab confirmed infection by seroconversion or viral culture

All definition: Lab confirmed infection by seroconversion, viral culture, or RT-PCR

RT-PCR definition: Lab confirmed infection by RT-PCR

Medical Officer’s comment: The ITTNAB population was a subset of the ITT population in which subjects with positive RT-PCR and/or viral culture at baseline were excluded. Seven subjects in the placebo group (3%) and four subjects in the oseltamivir group (2%) were found to have standard laboratory-confirmed influenza while on treatment, but this difference was not found to be statistically significant ($p=0.36$). There was also no significant difference between the treatment groups when the “all” definition was used.

There did appear to be a significant difference, however, between the treatment groups when the “RT-PCR” definition was used, with 7 subjects in the placebo group (3%) and 1 subject in the oseltamivir group (<1%) developing laboratory-confirmed influenza (p=0.032). Within the oseltamivir group, there were 4 subjects with laboratory-confirmed influenza by the “standard” definition, and 1 subject by the “RT-PCR” definition, indicating that the addition of serology and/or viral culture to RT-PCR resulted in more cases of influenza being diagnosed. This result suggests that the use of RT-PCR alone may be a more reliable method for detecting clinical influenza when compared with seroconversion or viral culture, or the latter two methods in combination with RT-PCR.

Using RT-PCR alone as a criterion for diagnosing clinical influenza is problematic. Firstly, the significance of influenza nucleic acid in respiratory secretions in the absence of clinical symptoms of the disease is unclear. This may represent a new, early influenza infection (assuming the RT-PCR was negative at baseline), or may represent asymptomatic viral shedding. Viral culture, though it may take longer than RT-PCR to return a result, may be more indicative of actively replicating virus. General medical practice dictates that clinical influenza be diagnosed when clinical symptoms are present, so it may be difficult to identify the significance of asymptomatic viral shedding.

The table below summarizes the ITTNAB subjects who developed laboratory-confirmed influenza based solely on RT-PCR, separated by illness category.

Table 9. Summary of ITTNAB Subjects with RT-PCR Confirmed Influenza by Illness Category

Laboratory Confirmed Influenza	Placebo N-231	Oseltamivir N=232
Clinical case (Fever + Symptoms)	7 (3%)	1 (<1%)
Infection with Fever	2 (1%)	0
Infection with Symptoms	3 (1%)	1 (<1%)
Asymptomatic	5 (2%)	2 (1%)
TOTAL	17 (7%)	4 (2%)

Medical Officer’s comment: When categorizing by illness, the differences between the treatment groups in the ITTNAB population were more significant, and there was a higher number of placebo subjects overall, in any illness category, who developed laboratory-confirmed influenza (17, or 7% in the placebo group, compared with 4, or 2% in the oseltamivir group, p~0.002) With the definition of a clinical case (fever with symptoms), there were more subjects in the placebo group (7, or 3%) compared with the oseltamivir group (1, or <1%) (p=0.032).

6.1.6 Other Endpoints

Exploratory Endpoints

Several exploratory analyses were conducted by the applicant, using the ITT population. Two analyses of laboratory confirmation of influenza by illness category using each of the standard and RT-PCR definitions were conducted using the ITTNAB population. As with the secondary analyses, there was no formal hypothesis testing for any of the exploratory analyses, and no sensitivity analyses or robustness checks were carried out by the applicant either.

These exploratory endpoints included viral culture-confirmed influenza, serologic-confirmed influenza, standard laboratory-confirmed influenza by illness categories based on all symptoms, and clinical course of influenza in subjects who developed laboratory-confirmed influenza. In addition, the differences between the treatment groups by laboratory confirmation methods (serology and virology) were also evaluated.

The endpoint of clinical course of influenza in subjects who developed laboratory-confirmed influenza yielded significant results. The change from baseline in viral antibody titers was assessed in all subjects with laboratory-confirmed influenza, of which there were 33 placebo subjects (excludes 3 for which paired baseline/post-baseline samples were not available) and 30 oseltamivir subjects. Among all subjects who were evaluated for change from baseline in antibody titers, 13 placebo subjects (39%) versus one oseltamivir subject (3%) had a <4-fold increase in antibody titers, while 20 placebo subjects (61%) versus 29 oseltamivir subjects (87%) had a ≥4-fold increase in antibody titer.

In subjects with laboratory-confirmed influenza in the ITT population, the geometric mean change from baseline in viral antibody titers was found by the applicant to be higher for subjects in the oseltamivir group compared with the placebo group (8.76-fold increase versus 4.43-fold change, respectively).

Medical Officer's comment: The serology results in the exploratory analysis appear to contradict the applicant's assertion that antibody response is non-specific in this immunocompromised population. For those subjects who developed laboratory-confirmed influenza, oseltamivir subjects clearly had a greater antibody response than placebo subjects. It is not clear why this would be the case, and may be due to multiple factors.

Please refer to the Microbiology/Virology Review for details on the laboratory methods used in the study.

6.1.7 Subpopulations

Subgroup Analyses

a. *Adults and Children*: All subjects except one in the oseltamivir group who were found by the applicant to have standard laboratory-confirmed influenza, were adults (≥ 13 years of age). Not enough pediatric subjects were enrolled to allow subgroup analysis by age of stratification.

b. *Solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT)*: The differences between the groups were not found to be statistically significant, and no further subgroup analyses were therefore conducted.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Tamiflu is an approved drug, and the approved doses (for weight) were used in this study. Exploration of dosing was not, therefore, an endpoint for this study.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The persistence of efficacy and/or tolerance was not assessed in this study.

6.1.10 Additional Efficacy Issues/Analyses

Medical Officer's comments: In conclusion, the primary analysis endpoint of this study was the incidence of laboratory-confirmed clinical influenza as assessed on treatment. This endpoint was selected by the applicant to determine if there was a difference in the incidence of influenza that is confirmed by laboratory methods, between immunocompromised subjects who are taking placebo, and those who are taking oseltamivir (Tamiflu) for prophylaxis. The primary endpoint was not met. However, some of the secondary and exploratory analyses provide supportive evidence of efficacy of Tamiflu. The majority of the assessments were conducted in the ITT population, rather than in the ITTNAB population. In earlier reviews, the Clinical Review team agreed that the most relevant population in studies of influenza prophylaxis was the group of subjects not shedding influenza virus at the time of study entry (ITTNAB).

Several issues are pertinent in light of the results of this study. Few subjects in either treatment group were found to have met the primary efficacy endpoint, namely the incidence of laboratory-confirmed clinical influenza (standard definition). The difference between the result in the placebo group and the oseltamivir group was not statistically significant, and although there was a trend towards such a difference, it was not conclusive.

The use of RT-PCR alone for lab-confirmation of influenza infection appeared to indicate greater efficacy of oseltamivir. Although RT-PCR is considered a more sensitive assay for viral material, diagnosis based on nucleic acid detection alone can be problematic, as discussed earlier, and clinical diagnosis of the disease involves the inclusion of symptoms. In the ITT population, the proportion of RT-PCR positive subjects confirmed by culture was not consistent across treatment arms. Among 48 samples that were found to be RT-PCR positive, 14 of 37 samples (38%) from the placebo subjects and 2 of 11 samples (18%) from the oseltamivir subjects were also viral culture positive, highlighting the problem with using RT-PCR alone for diagnosis. This method of diagnosis leads to detection of nucleic acid which may not represent replicating virus in a case of clinical influenza.

There are several possible reasons as to why the numbers of subjects with lab-confirmed influenza were low. The influenza rates during the years in which the study was conducted (2006-07 and 2007-08 flu seasons) may have been low to begin with, leading to a low attack rate, regardless of therapeutic intervention. This would prevent a significant difference from being noted between treatment groups, if there was one. Resistance to oseltamivir may have also played a role, leading to a greater number of subjects being susceptible to influenza infection with circulating strains. Oseltamivir-resistant H1N1 was known to be circulating in some areas of Europe during the 2007-08 flu season. Finally, the fact that about 40% of subjects in both treatment groups had been vaccinated against influenza may have reduced the population of subjects susceptible to infection.

[REDACTED] (b) (4)

. Whether there is a clinically relevant difference between the placebo and oseltamivir groups may depend upon the perceived risk of developing influenza recognized by a treating physician caring for an immunocompromised patient, who must decide on whether to administer oseltamivir for 12 weeks, based on the results of this study.

7 Review of Safety

Safety Summary of Study NV20235

7.1 Methods

Safety data for this NDA supplement were provided by the applicant in the form of electronic datasets that contained tables of clinical adverse events. As previously agreed with the Division, the applicant did not provide an Integrated Summary of Safety (ISS), but rather submitted the CTD Summary of Clinical Safety that incorporated relevant integrated analyses that are usually found in the ISS.

Narrative summaries and case report forms were provided for all subjects who experienced serious adverse events (both those deemed to be drug-related and those determined not to be drug related) in study NV20235. Narratives were provided, as requested by the Division, for all subjects who had one or more of the following: Deaths; all SAEs (drug-related and non-drug-related); and all drug-related AEs leading to withdrawal. Tabulations of AEs, SAEs, and study drug interruptions or discontinuations were compiled using the JMP Statistical Discovery Software (SAS Institute, Inc.).

The Safety population included all subjects who received at least one dose of study medication and had a post-baseline safety assessment.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation was conducted using the data generated from the trial under review, NV20235.

7.1.2 Categorization of Adverse Events

Subjects in the Safety Population were assigned to treatment groups as treated, for the purposes of analysis. AEs were categorized as “On Treatment” (occurring during the treatment period and up to and including 2 days after the last dose of study medication) or “Off Treatment” (occurring outside the treatment period, including later than 2 days following the last dose of study medication).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data from across studies other than NV20235 was not done.

7.2 Adequacy of Safety Assessments

The monitoring of clinical and laboratory safety parameters in this study was considered adequate in light of the fact that Tamiflu is an approved drug for which a significant amount of safety data are available from previously-reviewed prophylaxis (and treatment) protocols.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall Exposure of Safety Population

Data used to assess the overall exposure to study drug was taken from the subject diary, which noted the number of days of treatment taken. Those subjects who received less than 84 days (12 weeks) of treatment were categorized in one of three ways:

1. Subjects who did not complete treatment;
2. Subjects who did not complete the diary correctly; or
3. Subjects who were switched from daily treatment to treatment every other day due to creatinine clearance between 10 and 30 mL/min in adults, or between 10 and 30 mL/min/1.73m² for children.

The following table provides a summary of the extent of exposure to the trial medication:

Table 10. Summary of Extent of Exposure to Trial Medication (Safety Population)

	Placebo N=237	Oseltamivir N=238
Treatment Duration (days)		
1 – 7	6 (3%)	7 (3%)
8 – 14	7 (3%)	3 (1%)
15 – 21	6 (3%)	2 (<1%)
22 – 28	4 (2%)	2 (<1%)
29 – 35	3 (1%)	2 (<1%)
36 – 42	4 (2%)	1 (<1%)
43 – 49	2 (<1%)	5 (2%)
50 – 56	5 (2%)	0
57 – 63	5 (2%)	3 (1%)
64 – 70	2 (<1%)	1 (<1%)
71 – 77	8 (3%)	4 (2%)
78 – 84	185 (78%)	208 (87%)
> 85	0	0
Total Cumulative Dose (mg)*		
Mean	5373.4	5594.3
SD	1809.5	1685.7
Median	6300.0	6300.0
Min	7.0	7.0
Max	6375.0	6375.0
n	240	244

Modified from Table 33, p 75 of submitted study report

*For placebo: applicant eliminated 3 subjects who had total daily dose < 75 mg. For oseltamivir: applicant eliminated all subjects with TDD < 75 mg, but total does not equal 238 subjects

Medical Officer’s comment: The majority of subjects in each arm received study medication for 84 days (78% placebo group, 87% oseltamivir group.) Eight subjects received > 100% of the expected cumulative dose (6 in placebo group, 2 in oseltamivir group.) All 8 subjects received 101% of the cumulative dose, and were included in the efficacy and safety analyses. There is no note of these 8 subjects in the narratives provided (SAEs, discontinuations, or deaths), so it is concluded that none of these events occurred in association with this excessive cumulative dose of study medication. In the absence of information on other AEs, it is not possible to deduce whether this excessive cumulative dose was associated with any adverse events.

The applicant notes that several subjects were switched to treatment every other day due to creatinine clearance between 10 and 30 mL/min in adults or between 10 and 30 mL/min/1.73 M² for children (8 in placebo group, 7 in oseltamivir group.)

Medical Officer’s comment: The total cumulative dose for these subjects was lower than that for the remainder of subjects (mean cumulative dose for placebo subjects: 4050.0 (SD 1587.45); oseltamivir subjects: 3814.3 (SD 807.11).), which is expected given the lower frequency of dosing in these subjects with renal impairment.

Demographics of the Safety Population

A total of 475 subjects (placebo 237, oseltamivir 238) were included in the safety population. All had received, by definition, at least one dose of study drug and had at least one post-baseline safety assessment. The safety population excluded two subjects who were also excluded from the oseltamivir arm of the ITT population (87506/0720 and 87588/7117) due to a lack of efficacy data, and a lack of safety data. One subject (87531/2501) was randomized to receive placebo but received oseltamivir for the first 9 weeks (followed by placebo for 3 weeks), and was therefore switched from the placebo group to the oseltamivir group for the purposes of the safety analysis.

The following table summarizes the demographics of the safety population.

Table 11. Summary of Demographic Data of Safety Population

	Placebo N = 237	Oseltamivir N = 238
Age, overall (years) Mean	48.9	49.4

	Placebo N = 237	Oseltamivir N = 238
SD	15.67	15.47
Min-Max	1-74	1-76
n	237	238
Age by category (years)		
1 to 12		
Mean	5.9	6.2
SD	3.91	3.61
Min-Max	1-12	1-11
n	8	10
13-65		
Mean	47.8	47.2
SD	12.36	12.06
Min-Max	13-65	13-65
n	201	185
> 65		
Mean	69.6	68.9
SD	3.12	2.82
Min-Max	66-74	68-76
n	28	43
Sex		
Female	86 (36%)	74 (31%)
Male	151 (64%)	164 (69%)
n	237	238
Race		
Asian	3 (1%)	1 (<1%)
Black	15 (6%)	20 (8%)
White	219 (92%)	215 (90%)
Other	0	2 (<1%)
n	237	238
Ethnicity		
Hispanic	8 (3%)	3 (1%)
Non-Hispanic	229 (97%)	235 (99%)
n	237	238
Weight (kilograms)		
Mean	76.42	76.40
SD	20.36	21.27
Min-Max	10.0–133.5	9.0–144.0
n	236*	237*

	Placebo N = 237	Oseltamivir N = 238
Height (cm)		
Mean	167.8	168.7
SD	14.57	16.07
Min-Max	76 – 192	79 – 197
n	234*	235*
Influenza vaccination		
Yes	98 (41%)	93 (39%)
No	139 (59%)	145 (61%)
n	237	238

*Missing data

The safety population included subjects with a mean age of approximately 49 years (range, 1 to 76), with no significant difference between the placebo group and the oseltamivir group. Most patients were white (91% overall) and male (66% overall). The applicant notes that adults outnumbered children in both groups (229 versus 8 in the placebo group; 228 versus 10 in the oseltamivir group).

Medical Officer’s comment: A significant number of subjects in both treatment groups received influenza vaccination before enrollment into the study (41% placebo group; 39% oseltamivir group). This may have been one reason for the low number of subjects who were diagnosed with clinical influenza in this study

7.2.2 Explorations for Dose Response

There were no explorations made for dose response in this study.

7.2.3 Special Animal and/or In Vitro Testing

Tamiflu is an approved medication for treatment and prophylaxis of influenza, and no additional animal or in vitro testing was therefore conducted for this supplement.

7.2.4 Routine Clinical Testing

There was no routine clinical testing conducted.

7.2.5 Metabolic, Clearance, and Interaction Workup

There were no pharmacokinetic studies conducted in this study.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There were no evaluations for potential adverse events for similar drugs in the same drug class as oseltamivir.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in either the placebo group or the oseltamivir group during participation in the study. Two subjects died after being withdrawn from the study, both in the placebo group. Neither death was considered related to study medication by the investigator or the applicant. There were no deaths that occurred in the oseltamivir group at any time.

The line listing for these patients is noted below:

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Table 12. Death Listing (Treatment = Placebo)

Trial	Center	Subject ID	Age at time of death (years)	Sex	Last Treatment Day ³	Day of Death ⁴	Dose (mg)	Source ⁵	Description
NV20235	87547 (Madrid, Spain)	3809	58	F	55	84	Placebo OD	Primary	Relapsed acute myeloid leukemia;
NV20235	87589 (Toulouse, France)	1328	47	F	15	65	Placebo OD	Primary	Metastatic neoplasm, septic shock

¹Includes all deaths that occurred during the period of drug exposure and following discontinuation from study drug.

²Type of study drug, and dose of drug at time of discontinuation.

³Number of days on study drug before discontinuation.

⁴Number of days off drug at time of death.

⁵Source is clinical study report.

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Narratives of the two deaths in study NV20235:

Subject #: 87547/3809:

This 58 year old female with a history of hematopoietic stem cell transplantation for acute myeloid leukemia, two months prior to randomization, was started on placebo on January 18, 2008. The subject had engrafted at the time of randomization (baseline ANC > 500/mm³, platelet count = 20,000/mm³). Her baseline immunosuppressive medication was cyclosporin. Her past medical history was significant for recurrent bacterial infections, CMV antigenemia, and febrile neutropenia.

On day 14, the subject had adverse events of nasal congestion and decreased platelet count followed by anemia on day 15. The subject was treated with platelet and blood transfusions and developed the adverse event of peripheral edema on day 16. On day 22, the subject developed neutropenia. She was started on filgrastim (continued for 46 days). On day 38, she developed febrile neutropenia of moderate intensity (a serious adverse event), with an ANC of 520/mm³ (baseline 1300/mm³). On day 39, the subject developed relapsed acute myeloid leukemia of severe intensity (16 % blast cells in peripheral blood). She was treated with broad-spectrum antibiotics and lenalidomide (thalidomide derivative used for myelodysplastic syndrome). On day 41, the subject was found to be cytomegalovirus antigen positive. On study day 48, the subject developed gastrointestinal hemorrhage of life threatening intensity (a serious event) and hematochezia. On day 51, the event febrile neutropenia had resolved. The study medication was discontinued on day 55 due to the gastrointestinal hemorrhage. On day 59, the event resolved after treatment. The subject later had events of atrial fibrillation, febrile neutropenia, peripheral edema and respiratory tract infection, which was treated with antibiotics.

The subject died on day 83, due to the event of recurrent acute myeloid leukemia.

In the investigator's opinion, the events of acute myeloid leukemia recurrent, febrile neutropenia and upper gastrointestinal hemorrhage were unrelated to study medication.

Subject 87589/1328

The subject was a 47 year old female with a history of liver transplantation for alcoholic cirrhosis 13 years prior to randomization, who was started on placebo on January 29, 2008. Her baseline immunosuppressive medications were cyclosporin and mycophenolate mofetil. Her past medical history was significant for parathyroidectomy, thyroidectomy, laryngectomy, glossectomy for epidermoid carcinoma of the glosso-epiglottic groove, and hypertension.

On study day 3, the subject developed moderate bone pain (worsening of rachiolgia). She was treated with morphine and acetaminophen. On study day 9, the subject developed a non serious event of 'hepatic enzyme increased' which was mild in intensity [SGOT 75 U/L (Baseline SGOT 37 U/L, upper limit of normal 40 U/L), SGPT

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188 U/L (Baseline SGPT 59 U/L, upper limit of normal 55 U/L)]. This resolved spontaneously. The morphine and acetaminophen were stopped on day 14 when the bone pain had resolved. The same day a metastasis of malpighian type cancer (metastatic neoplasm) to lymph nodes and bones, was detected. The event was severe in intensity and remained unresolved. The subject was treated with fluorouracil, carboplatin, radiotherapy, prednisone, pamidronic acid, morphine, lenograstim, acetaminophen and fluid replacement.

On study day 15, study medication was discontinued, as the subject refused treatment.

On day 59, the subject developed severe lung infection and was started on amoxicillin/clavulanic acid. Two days later (day 61), she developed severe septic shock, neutropenia [ANC 1068/ μ L (baseline 6700/ μ L)], and acute renal failure [severe in intensity, with serum creatinine 304 μ mol/L (baseline 96 μ mol/L)]. She was started on broad-spectrum antibiotics, pressors, and antipyretics, and received hemodialysis and hemofiltration. On the same day, she developed severe acute respiratory distress syndrome and was treated with methyl prednisolone. On day 63, the subject developed atrial fibrillation which was moderate in intensity and was treated with amiodarone.

On day 65, the subject died due to septic shock. The events of neutropenia, acute renal failure and metastasis of malpighian type cancer were persisting at the time of death.

In the investigator's opinion, the events of metastatic neoplasm, neutropenia, acute renal failure and septic shock were unrelated to study medication.

Medical Officer's comments: One exclusion criterion for HSCT patients of note is "HSCT subjects with no evidence of engraftment (engraftment was defined as the point at which a subject could maintain a sustained absolute neutrophil count of > 500 cells/ μ L, and a sustained platelet count of \geq 20,000 cells/ μ L lasting \geq 3 consecutive days without transfusions)." One might argue that once HSCT recipients engraft, they remain significantly immunosuppressed for period of time (generally, Day 180 status-post transplantation is a time point at which most patients are not at as great a risk of developing opportunistic infections). Subject 87547/3809 appeared still to be quite ill upon enrolment, despite the fact that she had engrafted and fulfilled the study's inclusion criteria. Subjects who are selected for participation in such clinical trials are not expected to die early, unless mortality is an endpoint in the trial, which it was not in study NV20235.

Given the fact that both deaths occurred in subjects who were in the placebo group, and that the cause of death was deemed to be related to the underlying illness or another condition (septic shock for 87589/1328), the likelihood of an association with study drug is low. In the case of subject 87547/3809, study

medication was discontinued on study Day 55 due to a gastrointestinal hemorrhage of life-threatening intensity (a serious event) and hematochezia that began on Day 48, and likely an inability to tolerate and absorb the oral study drug as a result. Subject 87589/1328 refused to take the study medication, and it was discontinued on Day 15. The subject’s clinical status worsened on Day 59 when she developed a severe lung infection, and temporally and clinically, this event does not appear to be related to the study drug.

The two deaths appear to be consistent with the extent and nature of underlying disease and the known complications. The study drug did not appear to be related to the deaths in either case.

It should also be noted that there were no deaths in study NV20236 (NDA 21-087/S-035), a seasonal influenza prophylaxis study in children 1 to 12 years of age that was reviewed by Dr. Crewalk (see section 5.3).

7.3.2 Nonfatal Serious Adverse Events

A total of 82 SAEs were reported in study NV20235, with 49 SAEs occurring in subjects receiving placebo, and 33 in subjects receiving oseltamivir. The majority of SAEs occurred at a frequency of 1 per patient (< 1% overall). The following table shows those SAEs experienced by more than one patient.

The most frequently reported SAE was in the infections and infestations class (placebo 12/237 or 5%; oseltamivir 10/238 or 4%). The data for SAEs that occurred at a rate of ≥1% are shown in the table below:

Table 13. Summary of Serious Adverse Events by Super Class Term with Rate of Occurrence of ≥ 1%

	Placebo N = 237	Oseltamivir N = 238
Infections and Infestations	12 (5%)	10 (4%)
Nervous System Disorders	0	4 (2%)
Renal and Urinary Disorders	4 (1%)	2 (<1%)
Neoplasms Benign, Malignant and Unspecified	4 (1%)	1 (<1%)
General Disorders and Administration Site Conditions	1 (<1%)	3 (1%)
Injury, Poisoning and Procedural complications	4 (1%)	0
Gastrointestinal Disorders	4 (1%)	2 (<1%)
Respiratory, Thoracic and	3 (1%)	2 (<1%)

	Placebo N = 237	Oseltamivir N = 238
Mediastinal Disorders		
Musculoskeletal and Connective Tissue Disorders	3 (1%)	1 (<1%)
Immune System Disorders	3 (1%)	0

There were 32 SAEs noted by the applicant in the placebo group (occurring in 23 subjects, or 10%), and 20 SAEs noted in the oseltamivir group (occurring in 18 subjects, or 8%). The vast majority of SAEs each occurred in only one subject.

The table below summarizes the clinical adverse events (preferred terms) that occurred in each treatment group while on treatment.

Table 14. Summary of On-Treatment Serious Adverse Events

Clinical AE Preferred Term	Placebo N=237	Oseltamivir N=238
Abdominal symptom*	1 (<1%)	1 (<1%)
Arthritis bacterial	1 (<1%)	0
Bronchitis chronic	1 (<1%)	0
Cerebrovascular accident	0	1 (<1%)
Cholangitis	1 (<1%)	0
Cholecystitis	0	2 (1%)
Chronic allograft nephropathy	1 (<1%)	0
<i>Clostridium difficile</i> colitis	0	1 (<1%)
Deep venous thrombosis	0	1 (<1%)
Diabetes mellitus (inadequate control)	1 (<1%)	0
Dyspnea	0	1 (<1%)
Flank pain	0	1 (<1%)
Gastrointestinal hemorrhage**	1 (<1%)	1 (<1%)
Hypoglycemia	0	1 (<1%)
Intraductal papilloma of breast	1 (<1%)	0
Neutropenia	1 (<1%)	0
Pelvic fracture§	2 (1%)	0
Pneumonia	2 (1%)	1 (<1%)
Pyelonephritis acute	1 (<1%)	0
Pyrexia	0	2 (1%)
Renal cancer	1 (<1%)	0
Respiratory failure	2 (1%)	1 (<1%)
Respiratory tract infection***	2 (1%)	0
Sepsis¶	2 (1%)	1 (<1%)
Thalamus hemorrhage	0	1 (<1%)

Clinical AE Preferred Term	Placebo N=237	Oseltamivir N=238
Transplant rejection	1 (<1%)	0
Tubulointerstitial nephritis	1 (<1%)	0

*"Abdominal symptom" includes the terms abdominal symptom and constipation

**"Gastrointestinal hemorrhage" includes the terms gastrointestinal hemorrhage and upper gastrointestinal hemorrhage

***"Respiratory tract infection" includes the terms respiratory tract infection and upper respiratory tract infection

§ "Pelvic fracture" includes the terms pelvic fracture and pubic rami fracture

¶"Sepsis" includes the terms sepsis, septic shock, and *Staphylococcus* sepsis

Medical Officer's comment: The low frequency of SAEs noted in study NV20235 reflects the findings in other studies of oseltamivir that have been reviewed by DAVP. No new Tamiflu-related SAE signals were identified in this study population, in spite of the fact that the population was more ill than those previously studied. Similarly, no new SAE signals with Tamiflu were found in study NV20236 (Tamiflu for seasonal prophylaxis of influenza in children 1 to 12 years of age).

7.3.3 Dropouts and/or Discontinuations

The study reported a total of 51 subjects (11%) in the safety population who withdrew from the study prematurely. Thirty-three subjects were in the placebo group (7%) and 18 were in the oseltamivir group (4%). The applicant provided narratives for all subjects who had drug-related AEs leading to withdrawal. Fourteen subjects (6%) from the placebo group were withdrawn for reasons of safety, while 7 subjects (3%) were withdrawn from the oseltamivir group for reasons of safety. The table below summarizes the subjects who withdrew prematurely from the trial treatment, separated by reasons related to safety and those not related to safety.

Table 15. Summary of Subjects Prematurely Withdrawn from Trial Treatment (Safety Population)

Reason for Withdrawal	Placebo N = 237	Oseltamivir N = 238
Safety	14 (6%)	7 (3%)
Adverse Event	14 (6%)	7 (3%)
Non-Safety	19 (8%)	11 (5%)
Insufficient Therapeutic response	5 (2%)	1 (<1%)

Reason for Withdrawal	Placebo N = 237	Oseltamivir N = 238
Violation of Selection Criteria at Entry	-	1 (<1%)
Other Protocol Violation	1 (<1%)	1 (<1%)
Refused Treatment	7 (3%)	7 (3%)
Failure to return	5 (2%)	-
Withdrew	-	2 (<1%)
Other/Admin.	1 (<1%)	1 (<1%)
Total	33 (14%)	18 (8%)

*Adapted from Table 9, Research Report No. 1029450, page 46
 Percentages are based on N.

A greater number of subjects in the placebo group (14/237 or 6%) than in the oseltamivir group (7/238 or 3%) had their treatment prematurely withdrawn due to an adverse event. Subject 87515/7203 had his treatment withdrawn due to the development of influenza, and was reported also to have his treatment withdrawn due to an insufficient response.

The most frequently reported primary AEs that led to withdrawal from the study were gastrointestinal in the placebo group (two AEs of diarrhea, one AE of dyspepsia, one AE of gastrointestinal hemorrhage, accounting in total for 2% of AEs). Among the oseltamivir group, the most common AE reasons for withdrawal included one gastrointestinal AE of dyspepsia, accounting for <1% of AEs, and nervous system disorders (one AE of cerebrovascular accident, one AE of anxiety, and one AE of amnesia, accounting for 1% of AEs). There were no AEs related to the nervous system in the placebo group.

The following table shows the individual subjects who withdrew for adverse events, both from the placebo group and from the oseltamivir group. The table summarizes the reasons for withdrawal:

Table 16. Summary of Subjects Withdrawn for Safety Reasons

Subject #	Age (years)	Gender	Day of Treatment Withdrawal	Relation of Withdrawal to Study Drug	SAE – Preferred Term
PLACEBO					
87506/0701	56	M	2	Possibly related	Dyspepsia
87506/0721	48	M	16	Unrelated	Pneumonia
87515/7203	62	M	30	Unrelated	Influenza (influenza A)
87527/3002	48	M	22	Possibly related	Asthenia (weakness)

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Subject #	Age (years)	Gender	Day of Treatment Withdrawal	Relation of Withdrawal to Study Drug	SAE – Preferred Term
87547/3809*	58	F	55	Unrelated	Upper gastrointestinal hemorrhage
87551/6213	51	F	23	Unrelated	Pelvic fracture
87557/6402	66	F	15	Possibly related	Eyelid edema
87557/6404	52	M	4	Possibly related	Upper respiratory tract infection
87559/3218	65	M	43	Unrelated (both)	Bronchitis chronic; Blood creatinine increased
87565/0809	61	M	5	Possibly related	Diarrhea
87573/7404	56	F	22	Unrelated	Hypogammaglobulinemia
87581/1202	66	F	26	Possibly related	Diarrhea
87588/7102	60	M	53	Unrelated	Interstitial nephritis
87591/8602	56	F	62	Unrelated (all)	Pneumonia; GI hemorrhage; Renal cancer
87614/5770	58	F	14	Related	Transplant rejection (acute cellular rejection)
OSELTAMIVIR					
87523/1541	41	M	28	Possibly related	Dyspepsia
87524/1605	64	M	59	Unrelated	Cerebrovascular accident; Abdominal symptom (unclear)
87527/3005	40	M	27	Possibly related	Anxiety
87529/0406	37	F	6	Remotely related	Chills
87534/0506	45	F	44	Possibly related	Amnesia
87591/8606	56	M	31	Unrelated	Esophageal adenocarcinoma
87614/5767	71	M	17	Unrelated	Acute left thalamic hemorrhage

* Fatal SAE

Medical Officer’s comment: Narratives for 15 subjects in the placebo group were provided in the study CSR, but only 14 subjects in this category were accounted for in the database; the number of subjects in the oseltamivir group narratives (7) is consistent with that in the database.

Although infections and infestations were the most common causes of SAEs by system organ class (SOC), reasons for discontinuation from a safety standpoint, were more diverse. There were more discontinuations in the placebo group, and only three appeared to be related to infection (influenza A in subject 7203, upper respiratory tract infection in subject 6404, and pneumonia in subject 8602). There were no infections noted as causes of discontinuation in the oseltamivir group, and only one gastrointestinal cause (dyspepsia in subject 1541). The causes deemed “possibly related” to the study drug (amnesia, anxiety, and dyspepsia) have not been noted as frequent or infrequent adverse events that occur as a result of Tamiflu use (treatment or prophylaxis). Of note, anxiety has been reported as a psychiatric AE during post marketing use of Tamiflu

7.3.4 Significant Adverse Events

Several subjects had their study medication dosing frequency changed from daily to every other day due to creatinine clearance levels of ≤ 30 mL/min (8 placebo subjects and 7 oseltamivir subjects).

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The “On Treatment” period included the period of time on the study medication as well as 2 days after the last day of treatment. The applicant notes in their analysis that the number and percentage of subjects who experienced at least one AE while on study treatment was similar in both treatment groups (placebo 137 [58%], oseltamivir 132 [55%].) The most commonly reported AEs in both treatment groups were gastrointestinal disorders (placebo 22%, oseltamivir 21%), followed by infections and infestations (placebo 19%, oseltamivir 18 %.)

A summary of AEs reported through the study period by body system category is shown in Table 17 below.

Table 17. Summary of On-Treatment Adverse Events

Body System Adverse Event	Placebo N = 237	Oseltamivir N = 238
Blood and Lymphatic System Disorders	6 (3%)	6 (3%)
Cardiac System Disorders	5 (2%)	4 (2%)
Ear and Labyrinth Disorders	0	4 (2%)
Endocrine System Disorders	2 (<1%)	1 (<1%)
Eye Disorders	6 (3%)	6 (3%)
Gastrointestinal System Disorders	53 (22%)	49 (21%)
General Disorders and Administration Site Conditions	27 (11%)	28 (12%)
Hepatobiliary System Disorders	2 (<1%)	2 (<1%)
Immune System Disorders	6 (3%)	7 (3%)
Infections and Infestations	45 (19%)	42 (18%)
Injury, Poisoning and Procedural Complications	10 (4%)	6 (3%)
Investigations	17 (7%)	9 (4%)
Metabolism and Nutrition Disorders	12 (5%)	9 (4%)
Musculoskeletal and Connective Tissue Disorders	21 (9%)	16 (7%)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	4 (2%)	4 (2%)
Nervous System Disorders	21 (9%)	21 (9%)
Psychiatric Disorders	4 (2%)	5 (2%)
Renal and Urinary Disorders	7 (3%)	8 (3%)
Reproductive System and Breast Disorders	4 (2%)	2 (<1%)
Respiratory, Thoracic and Mediastinal Disorders	30 (13%)	14 (6%)
Skin and Subcutaneous Tissue Disorders	9 (4%)	10 (4%)
Vascular Disorders	15 (6%)	12 (5%)

The majority of AEs that occurred while on treatment were of mild severity (340/650). The remainder were moderate (258/650), severe (50/650) or life-threatening (2/650). Most of the adverse events that occurred off treatment were mild in intensity (130/265), and there was a lesser number of AEs of moderate intensity (97/265). There were a

smaller number of severe events (36/265) and the two life-threatening AEs previously mentioned.

Specific AEs that were reported in > 2% of each treatment group for the On Treatment study period are summarized in the table below. Of note, the Preferred Terms were selected from the MeDRA medical dictionary by the applicant.

Table 18. 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%)

Percentages base on N for each treatment group.

Medical Officer’s comment: The Tamiflu label cites rates of AEs in adult patients in treatment and prophylaxis studies. AEs that occurred at an incidence of ≥ 1% included nausea without vomiting, vomiting, and diarrhea. AEs for adult subjects (adolescent, healthy adults and elderly) who participated in phase III prophylaxis studies for up to 6 weeks were qualitatively similar to those seen in treatment studies, and included nausea without vomiting, headache, and fatigue.

The AEs noted in the prophylaxis study under review are similar in nature and in frequency.

Treatment-Related Adverse Events

The applicant notes that the relationship of each AE to study treatment was assessed by the investigator as unrelated, remotely related, possibly related, or probably related. Most AEs on treatment were deemed by the investigators as being unrelated to study medication. The most frequently reported treatment-related AEs were gastrointestinal disorders. Table 19 shows the relatedness of the AEs with the treatment, by body system, according to the investigators. The applicant notes also that there were no apparent differences between treatment groups in the incidence of any treatment-related AE on treatment.

Table 19. Summary of On Treatment Adverse Events by Body System

Body System/Adverse Event	Placebo N=237			Oseltamivir N=238		
	Total	Not Related	Related	Total	Not Related	Related
ALL BODY SYSTEMS Total with at least one AE	315	253	62	272	196	76
Total number of AEs	361	291	70	323	274	49
	Subjects with at least one AE			Subjects with at least one AE		
Gastrointestinal Disorders	56	34	22	52	35	17
Infections and Infestations	46	44	2	43	38	5
Administration Site Conditions	30	22	8	30	23	7
Respiratory, Thoracic and Mediastinal Disorders	31	26	5	15	13	2
Nervous System Disorders	21	14	7	20	19	1
Musculoskeletal and Connective Tissue Disorders	21	19	2	16	16	0
Vascular Disorders	15	12	3	12	8	4
Investigations	18	13	5	9	7	2
Metabolism and Nutrition	12	11	1	9	8	1

Body System/Adverse Event	Placebo N=237			Oseltamivir N=238		
Disorders						
Skin and Subcutaneous Tissue Disorders	9	8	1	10	8	2
Injury, Poisoning and Procedural Complications	10	9	1	6	5	1
Renal and Urinary Disorders	7	6	1	8	8	0
Immune System Disorders	6	5	1	7	6	1
Blood and Lymphatic System Disorders	6	5	1	6	6	0
Eye Disorders	6	5	1	6	6	0
Psychiatric Disorders	4	3	1	4	4	0
Cardiac Disorders	5	5	0	4	4	0
Neoplasms Benign, Malignant and Unspecified	4	4	0	4	4	0
Reproductive System and Breast Disorders	4	4	0	2	1	1
Ear and Labyrinth Disorders	0	0	0	4	4	0
Hepatobiliary Disorders	2	2	0	2	2	0
Endocrine Disorders	2	2	0	1	1	0

Adapted from table in CSR, page 730

“Related” category includes remotely-, possibly-, and probably related AEs

Medical Officer’s comment: After reviewing the safety data submitted in support of this sNDA, this Medical Officer recommends for safety labeling that the safety profile of the drug in immunocompromised patients taking Tamiflu be noted to be consistent with that previously seen in other clinical trials of prophylaxis with Tamiflu

7.4.2 Laboratory Findings

All 475 subjects in the safety population had laboratory parameters measured on Day 1 (date of the first dose of study drug; could be performed concurrent with the baseline visit), while the numbers decreased slightly over the remainder of the study: 449 subjects (95%) had laboratory assessments at Day 84 or withdrawal (end-of-treatment). Unscheduled labs were drawn on 23 subjects (5%).

The applicant notes in the CSR that mean laboratory values for most variables were within the normal range for both groups, and showed little variation over time. The mean red cell count values were consistently below the normal range for the oseltamivir group (4.50 to 5.30×10^{12} cells/L) throughout the study (i.e. baseline, 4.46×10^{12} cells/L; day 84, 4.47×10^{12} cells/L). In addition, mean values for RBC counts did not change between baseline and day 84. The applicant states that similar mean RBC counts were observed for the placebo group at several time points throughout the study.

No consistent patterns with regard to grade shifts were noted for particular laboratory variables. There were only five subjects who had changes from normal (Grade 0) at baseline to grade 3 or grade 4, and four of these were in ALT with one in hemoglobin, as shown in the table below:

Clinical Review
 {Tafadzwa Vargas-Kasambira, MD, MPH}
 {NDA 21-087/S-049, NDA 21-246/S-017
 {Tamiflu® (oseltamivir phosphate)}

Table 20. Summary of Subjects with Grade 3 or Grade 4 Shifts in Adverse Events

Subject Number	Treatment Group	Grade Shift Category	Laboratory Parameter	Lab Value Day 1	Lab Value Day 7	Lab Value Day 28	Lab Value Day 56	Lab Value Day 84/WD	Lab Value Follow-up
87551/6211	Placebo	0 to 3	ALT (U/L)§	30	41	46	256	34	-
87523/1514	Placebo	0 to 4	ALT (U/L)	20	18	104	774	57	13
87614/5753	Oseltamivir	0 to 3	Hemoglobin (g/L)●	120	119	113	79	110	84
87523/1541	Oseltamivir	0 to 4	ALT (U/L)	23	17	-	-	553	14
87523/1520*	Oseltamivir	0 to 3	ALT (U/L)	25	24	NVR	138	29	17

*Subject 87523/1520 also had unscheduled lab: ALT 31

§ Normal range of ALT values, per applicant criteria: 11-37 U/L

● Normal range of Hemoglobin values, per applicant criteria: 116-154 g/L

NL = Normal value

Medical Officer's comment: Data for subject 87523/1541 at Days 28 and 56 are not present in the database, although there are values given in the narratives. This Medical Officer has elected to enter only the data available in the database.

Two of the four subjects with laboratory grade shifts were in the placebo group, and the other two were in the oseltamivir group. Their characteristics were as follows:

- Subject #6211 was a liver transplant recipient with diabetes mellitus who experienced a sudden shift to grade 3 for ALT on Day 56, and this value had normalized by Day 84.
- Subject #1514 was a HSCT recipient who experienced no AEs, but had an elevation in ALT on Day 28 (to 128 U/L), and reached a peak at Day 56, as shown in the table. The labs had normalized by the follow-up visit.
- Subject #1541 was an HSCT recipient who discontinued treatment prematurely on day 28 due to the AE of dyspepsia. The subject did not have ALT values for Days 28 and 56, and peaked at the Day 84 visit; the lab had normalized by the follow-up visit.
- Subject #1520 was an HSCT recipient with chronic GVHD whose ALT peaked at Day 56, and had normalized by the subsequent visit at Day 84.

As noted by the applicant the oseltamivir subject who had a grade 3 shift in hemoglobin (subject #5753) was a kidney transplant recipient with diabetes mellitus who developed the serious AE of severe gastroenteritis on day 58. The subject had hemoglobin concentration at the lower limit of the reference range, and remained below the lower limit of the reference range through Day 112.

Medical Officer's comment: The elevated ALT values for the four patients, while on treatment, returned to normal at the end of the treatment period or during follow-up. There were no subjects with persistently elevated ALT values after treatment was completed. In the single subject with low hemoglobin during treatment, the nadir occurred on day 56, and had still not completely normalized by the follow-up visit off treatment. The possibility of an interaction between oseltamivir and concomitant medications causing these lab shifts was not evaluated, and no further exploration on alternate causes of the lab changes was carried out.

7.4.3 Vital Signs

As noted by the applicant, vital signs showed little variation over time in either the placebo or the oseltamivir group.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not obtained as a routine part of the assessments carried out in this study.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted.

7.4.6 Immunogenicity

The applicant discusses baseline viral antibody titers in the ITT population in the submission. Influenza antibody titers $\geq 1:40$ are considered protective. For each viral subtype discovered (Influenza A, H3N2; influenza A, H1N1; and influenza B), a higher percentage of placebo subjects had protective viral antibody titers. A higher percentage of subjects had influenza A H3N2 titers $\geq 1:40$ compared with H1N1 and influenza B titers $\geq 1:40$.

Medical Officer's comment: Given the fact that a lower percentage of subjects in the oseltamivir group had protective titers against influenza A, it is possible that this group was more susceptible to infection with the virus, and this may have reduced the effect seen with the use of Tamiflu prophylaxis. Please see Efficacy section for further details.

7.5 Other Safety Explorations

The majority of AEs on treatment were deemed by the investigators to be unrelated to study medication. The most frequent treatment-related AEs (i.e. remotely-, possibly-, or probably-related) were gastrointestinal disorders, and these included diarrhea, nausea, and vomiting. According to the sponsor, there were no apparent differences between treatment groups in the incidence of any treatment-related AEs while on treatment.

7.5.1 Dose Dependency for Adverse Events

This aspect was not assessed.

7.5.2 Time Dependency for Adverse Events

Adverse events were assessed throughout the "on treatment" period. No specific time-dependency was identified

7.5.3 Drug-Demographic Interactions

There were 167 males and 89 females who developed at least one AE whilst on treatment. The mean number of AEs for males was 2.0 and 3.0 for females

7.5.4 Drug-Disease Interactions

There were 206 SOT recipients and 50 HSCT recipients who developed at least one AE whilst on treatment. The mean number of AEs for SOT recipients was 2.3, and the mean number of AEs for HSCT recipients was 3.4

Medical Officer’s comment: HSCT recipients had a higher mean number of AEs than SOT recipients. One possible reason may be that there was a shorter period between transplantation and enrollment in the study in the HSCT recipients compared with the SOT recipients (see Table 6), and the difference may have had more to do with the HSCT subjects being more ill at baseline, rather than having more treatment-related AEs.

7.5.5 Drug-Drug Interactions

Many patients were on more than one other drug during the study, including immunosuppressants. No formal assessment was made of the drug interactions between Tamiflu and these other drugs.

7.6 Additional Safety Evaluations

Tamiflu is an approved drug, and this submission did not, therefore, contain any pre-clinical data or analysis. Section 7.6 is therefore not applicable.

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

There are no additional submissions that have been received from the applicant. There are no further safety issues other than those that have been previously discussed.

In conclusion, the use of Tamiflu once daily for 12 weeks as prophylaxis in the setting of immune compromise was found to be safe and well-tolerated. The safety profile was acceptable in both HSCT and SOT subjects, and in all age groups. The safety results of the study appear to be fairly consistent with the known safety profile of oseltamivir. No update in the safety information of the label is warranted.

Clinical Review
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{NDA 21-087/S-049, NDA 21-246/S-017
{Tamiflu® (oseltamivir phosphate)}

8 Postmarket Experience

DAVP and OSE are continuously monitoring post-marketing AEs and reviewing specific events as needed.

9 Appendices

9.1 Literature Review/References

1. Gross PA, Russo C, Dran S, Cataruozolo P, Munk G, Lancey SC. Time to earliest peak serum antibody response to influenza vaccine in the elderly. Clin Diagn Lab Immunol. 1997;4(4):491-2
2. Hara M, Tanaka K, Hirota Y. Immune response to influenza vaccine in healthy adults and the elderly: association with nutritional status. Vaccine 2005;23(12):1457-63
3. Huzley D, Neifer S, Reinke P, et al. Routine immunization in adult renal transplant recipients. Transplantation 1997;63:839
4. Blumberg EA, Albano C, Pruett T, et al. The immunogenicity of influenza virus vaccine in solid organ transplant recipients. Clin Infect Dis 1996;22:295
5. *MMWR Recommendations and Reports*, "[Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients: Recommendations of CDC, the Infectious Diseases Society of America, and the American Society of Blood and Marrow Transplantation](#)". Oct 20, 2000/49(RR10);1-128
6. Gross PA, Russo C, Dran S, Cataruozolo P, Munk G, Lancey SC. Time to earliest peak serum antibody response to influenza vaccine in the elderly. Clin Diagn Lab Immunol. 1997;4(4):491-2
7. Hara M, Tanaka K, Hirota Y. Immune response to influenza vaccine in healthy adults and the elderly: association with nutritional status. Vaccine 2005;23(12):1457-63

9.2 Labeling Recommendations



(b) (4)

Clinical Review
{Tafadzwa Vargas-Kasambira, MD, MPH}
{NDA 21-087/S-049, NDA 21-246/S-017
{Tamiflu® (oseltamivir phosphate)}



9.3 Advisory Committee Meeting

There will be no Advisory Committee meeting convened for this sNDA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21087	SUPPL-49	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES

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/s/

TAFADZWA S VARGAS-KASAMBIRA
02/22/2010

LINDA L LEWIS
02/22/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21-087

Applicant: Hoffmann-La Roche Inc.

Stamp Date: August 10, 2009

Drug Name: Tamiflu® (oseltamivir phosphate) capsules

NDA/BLA Type: Priority Review

Completion Date: September 28, 2009

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic submission (sponsor received waiver for eCTD format 2/06/2009 to 12/31/2009)
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	Contains CTD Summary of Clinical Safety, as agreed in pre-NDA interactions with FDA
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Contains CTD Summary of Clinical Efficacy, as agreed in pre-NDA interactions with FDA
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?		X		
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: NV20235	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>Study Title: A double-blind, randomized, placebo-controlled, multicenter trial of oseltamivir for the seasonal prophylaxis of influenza in immunocompromised patients Sample Size: Randomized – 477 Arms: Placebo, 238; oseltamivir, 239 Location in submission: Electronic Archive Copy (Folder) - clinstat</p> <p>Study Number: NV20236 Study Title: An open-label multicenter trial of oseltamivir for the seasonal prophylaxis of influenza in children Sample Size: Enrolled - 52 Arms: Single arm Location in submission: Electronic Archive Copy (Folder) - clinstat</p>				
EFFICACY					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Study #1: NV20235 (b) (4)</p> <p>Study #2: NV20236 Indication: Six-week seasonal prophylaxis of influenza in pediatric patients between 1 and 12 years of age</p>	X			<p>Not an initial NDA, adequate for sNDA for additional population.</p> <p>Controlled study not requested; safety study requested and will rely on extrapolation for adult efficacy.</p>
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Product is approved. sNDA is submitted for approval of expanding target population.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			See #9 above.
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	Product is approved. sNDA is submitted for approval of new indications.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	Product is approved.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	Product is approved; no special studies were requested.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Please provide the location of the coding dictionary in the supplements. The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim). If the coding dictionary was not included in the supplements, please submit.

Tafadzwa Vargas-Kasambira, M.D., M.P.H.

 Reviewing Medical Officer

September 24, 2009

 Date

 Clinical Team Leader

 Date

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

/s/

TAFADZWA S VARGAS-KASAMBIRA
09/28/2009

LINDA L LEWIS
09/28/2009

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021087/S-049

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

<u>SUBMISSION/TYPE</u>	<u>SDN</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
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:

Nonproprietary/USAN:

Code Names/#'s:

Chemical Type/

Therapeutic Class:

TAMIFLU® Capsules

oseltamivir phosphate

Ethyl ester prodrug

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

NDA 21-087 / SLR-048, SES-049

Page 2 of 14

NDA 21-246 / SLR-034, SES-035

TAMIFLU® (oseltamivir phosphate) Capsules, 75mg

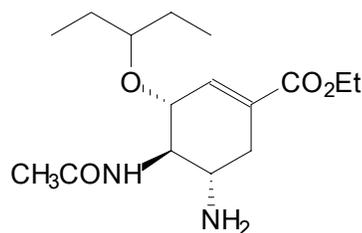
TAMIFLU® (oseltamivir phosphate) for Oral Suspension, 12mg/mL

Hoffmann-La Roche Inc.

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: C₁₆H₂₈N₂O₄·PO₄
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/JS Hathaway
ONDQA/DPE/ChemPAL/SDe
ONDQA/DPE/ChemBranchChf/HPatel

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/

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-049

MICROBIOLOGY REVIEW(S)

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW**

NDA: 21087 SE-049/21246 SE-035 SDN 378 DATE REVIEWED: 1/25/10

Reviewer: Damon J. Deming, Ph.D.

Date Submitted: 08/10/09

Date Assigned: 08/12/09

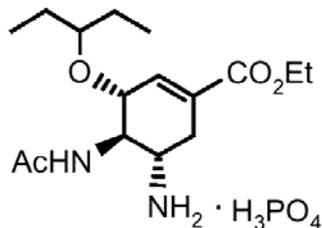
Date Received: 08/10/09

Sponsor: Hoffman-LaRoche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199
S. Elizabeth Lucini, Pharm.D.
Program Manager
973-235-6141
973-562-3700 (FAX)
elizabeth.lucini@roche.com

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:



OSELTAMIVIR PHOSPHATE

Molecular formula: C₁₆H₂₈N₂O₄ (free base)

Molecular weight: 312.4 for the free base, 410.4 for the phosphate salt

Drug category: Antiviral

Indication: [REDACTED] (b) (4) and
6 week prophylaxis in children between 1 and 12 years of age.

Dosage Form/Route of administration: adults and children ≥ 13 years: 75 mg/Oral
children 1-12 years: 30-75 mg based on body mass/Oral

Supporting documents: IND 53,093; NDA 21087; NDA 21246

Abbreviations: HA, hemagglutinin; HAI, hemagglutination inhibition; HSCT, hematopoietic stem cell transplantation; ITT, intent to treat; ITTNAB, intent to treat and virus negative at baseline; MDCK, Madin-Darby Canine Kidney Cells; NA, neuraminidase; NAI, neuraminidase inhibition; RT-PCR, reverse transcriptase polymerase chain reaction; SOT, solid organ transplantation;

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW

NDA: 21087 SE-049/21246 SE-035 SDN 378 DATE REVIEWED: 1/25/10

EXECUTIVE SUMMARY

Antiviral drugs are among the few therapeutic and prophylactic treatments for seasonal and pandemic influenza virus infections. There are two approved classes of anti-influenza drugs: the M2 ion inhibitors, or adamantanes, and the neuraminidase inhibitors (NAIs). The adamantanes include amantadine (NDA 016020, 016023, 017118, and 018101) and rimantadine (NDA 019649 and 019650), approved for the treatment of uncomplicated influenza A virus infection in patients ≥ 1 year of age in October 1966 and September 1993, respectively. The NAIs include zanamivir (NDA 021036) and oseltamivir phosphate (NDA 021087 and 21246). Zanamivir was approved for treatment of uncomplicated influenza A and B virus infection in patients ≥ 7 years of age in July 1999, and oseltamivir phosphate was approved for treatment of uncomplicated influenza A and B virus infections in patients ≥ 1 year of age in October 1999. However, the emergence of adamantane-resistant influenza strains has rendered the adamantanes ineffective against currently circulating strains ([Deyde et al., 2007](#), [Dharan et al., 2009](#), [CDC, 2010](#)). The novel 2009 (swine) H1N1 pandemic strain, which represented 98% of the subtyped influenza A viruses reported for the 2009/2010 influenza season, also harbored the adamantane resistance-associated substitution, M2 S31N, but retained susceptibility to NAIs ([CDC, 2010](#)).

Neither of the neuraminidase inhibitors has been approved for prophylaxis of influenza virus infection in immunocompromised and pediatric populations. Hoffman-LaRoche, Inc. has submitted the results of 2 studies as part of a supplemental application to fulfill this unmet medical need. The results of two clinical studies are included: Study NV20235, "A double-blind, randomized, placebo controlled, multi-center trial of oseltamivir for the seasonal prophylaxis of influenza in immunocompromised patients," and Study NV20236, "An open-label multi-center trial of oseltamivir for the seasonal prophylaxis of influenza in children."

The lower than expected rates of influenza virus infection confounded the efficacy and resistance analyses of both Study NV20235 and Study NV20236. In Study NV20235, 5/237 (2.1%) subjects from the oseltamivir-treated arm and 7/238 (2.9%) subjects from the placebo-treated arm were confirmed with clinical influenza, defined as oral temperature $> 32.7^{\circ}\text{C}$ plus cough and/or coryza within 24 hours of fever, plus either a positive virus culture or a 4-fold increase in virus antibody titer from Baseline. The difference was not statistically significant. When RT-PCR for influenza virus matrix RNA was used for the laboratory confirmation of clinical influenza infection, 1/232 (0.4%) subjects in the oseltamivir-treated arm and 7/231 (3.0%) subjects were scored positive for clinical influenza among subjects who were not RT-PCR positive at Baseline.

As defined in the protocol for Study NV20235, resistance monitoring was limited to viruses cultured from samples taken at consecutive time points. No samples from the oseltamivir-treated subjects met those criteria. Furthermore, no virus was detected in any sample collected during Study NV20236. DAVP requested that the sponsor determine if the influenza strains detected by RT-PCR during NV20235 contained the known resistance-conferring substitution, NA H275Y. The analyses indicated that prophylaxis failures could not be attributed to infection with a circulating oseltamivir-resistant variant or the selection of oseltamivir resistance during prophylaxis.

1 Recommendations

1.1 Recommendation and Conclusion on Approvability

The amendments to the Tamiflu[®] labeling proposed by the applicant to include safety information related to the use of oseltamivir phosphate for 12-week prophylaxis in immunocompromised subjects and 6-week prophylaxis in pediatric subjects are acceptable.

1.2 Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management

There are no Phase 4 commitments for this supplemental submission.

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2 Summary of Clinical Microbiology Assessments

N/A

3 Administrative

3.1 Reviewer's Signature

Damon J. Deming, Ph.D.
Microbiologist, HFD-530

3.2 Concurrence

_____ Date _____
HFD-530/J. O'Rear /TL Micro

cc:

HFD-530/NDA
HFD-530/Division File
HFD-530/RPM/Thompson

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4 Microbiology Review

4.1 Introduction and Background

Antiviral drugs and annual vaccinations are the only means of prophylaxis for seasonal influenza virus infections. In the case of newly emergent pandemic strains that are not antigenically similar to vaccine strains, antiviral drugs represent the sole therapeutic option. There are two approved classes of anti-influenza drugs: the M2 ion inhibitors, or adamantanes, and the neuraminidase inhibitors (NAIs). The adamantanes include amantadine (NDA 016020, 016023, 017118, and 018101) and rimantadine (NDA 019649 and 019650), approved for the treatment of uncomplicated influenza A virus infection in patients ≥ 1 year of age in October 1966 and September 1993, respectively. The NAIs include zanamivir (NDA 021036) and oseltamivir phosphate (NDA 021087 and 21246). Zanamivir was approved for treatment of uncomplicated influenza A and B virus infection in patients ≥ 7 years of age in July 1999, and oseltamivir phosphate was approved for treatment of uncomplicated influenza A and B virus infections in patients ≥ 1 year of age in October 1999. The adamantanes are effective against susceptible influenza A strains, while the NAIs offer broader protection against both influenza A and B viruses. However, the emergence of adamantane-resistant influenza strains has rendered the adamantanes ineffective against currently circulating variants ([Deyde et al., 2007](#), [Dharan et al., 2009](#), [CDC, 2010](#)). From the 1999-2000 up to the 2007-2008 influenza seasons, less than 1% of the isolates tested worldwide demonstrated reduced susceptibility to NAIs ([Dharan et al., 2009](#)). The number of oseltamivir resistant H1N1 isolates rose significantly in the 2007-2008 season to ~19% due to the development of the H275Y substitution. Reports for the 2008-2009 influenza season found even higher oseltamivir resistance rates for in the U.S. (99.5%), indicating that oseltamivir was in danger of being lost as an effective therapy against seasonal influenza H1N1 strains. The novel 2009 (swine) H1N1 pandemic strain, which represented 98% of the subtyped influenza A viruses reported from September 1, 2009 to the third week of January, 2010, retained susceptibility to NAIs but harbored the adamantane resistance-associated substitution, M2 S31N ([CDC, 2010](#)).

Neither of the neuraminidase inhibitors has been approved for prophylaxis of influenza virus infection in immunocompromised and pediatric populations. Hoffman-LaRoche, Inc. has submitted the results of 2 studies as part of a supplemental application to fulfill this unmet medical need. The results of two clinical studies are included:

Study NV20235: "A double-blind, randomized, placebo controlled, multi-center trial of oseltamivir for the seasonal prophylaxis of influenza in immunocompromised patients." In the November 17, 2000 approval letter for the use of oseltamivir for prophylaxis of influenza for adults and adolescents 13 years of age and older (NDA 21-087/S-002), the FDA requested that Roche investigate the efficacy and safety of oseltamivir for the prevention of influenza virus infection in immunocompromised subjects. Study NV20235 was designed to fulfill that post approval commitment, and on November 8, 2006, the protocol was submitted under IND 053093.

Study NV20236: "An open-label multi-center trial of oseltamivir for the seasonal prophylaxis of influenza in children." In the December 21, 2005 approval letter for the use of oseltamivir for prophylaxis of influenza for children 1 year to 12 years of age, the FDA requested that Roche collect and submit data in 40 to 50 subjects in this pediatric population for a period of up to 6 weeks in a seasonal prophylaxis setting. Study NV20236 was designed to fulfill this post approval commitment, and on November 8, 2006, the protocol was submitted under IND 053093.

The key virology issue that arose during the review of this supplemental application concerned the absence of a resistance analysis, which was the result of a lower than expected influenza virus infection rate. This was a concern because immunosuppressed patients may shed virus for prolonged periods, potentially increasing the chances for selection of oseltamivir resistance ([Ison et al., 2006](#); [MMWR, Aug 21, 2009](#)). As defined in the protocol for Study NV20235, resistance monitoring (i.e., testing clinical isolates for oseltamivir susceptibility) was limited to viruses cultured from samples taken at consecutive time points. Unfortunately, no samples from the oseltamivir-treated subjects met those criteria. Furthermore, no virus was detected in any sample collected during Study NV20236. DAVP requested that the sponsor determine if the influenza strains detected by RT-PCR during NV20235 contained

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the known resistance-conferring substitution, NA H275Y. The analyses indicated that prophylaxis failures could not be attributed to infection with a circulating oseltamivir-resistant variant or the selection of oseltamivir resistance during prophylaxis.

4.1.1 Important Milestones in Product Development

NDA 21087 received FDA approval on October 27, 1999 for Tamiflu[®] capsule treatment of uncomplicated acute illness due to influenza virus infections in adults who have been symptomatic for no more than two days. NDA 21246 received FDA approval on December 14, 2000 for Tamiflu[®] oral suspension for the treatment of uncomplicated acute illness due to influenza virus infections in patients older than one year of age who have been symptomatic for no more than two days.

The following supplements have also received approval:

- November 17, 2000: NDA 21-087/S-002 for prophylaxis of influenza in adults and adolescents 13 years and older
- December 21, 2005 NDA 21-087/S-030 and NDA 21-246/S-017 for prophylaxis of influenza for patients between 1-12 years of age

4.1.1.1 Methodology

STUDY NV20235 was a prospective, parallel group, stratified, randomized, double-blind, placebo-controlled, multicenter, Phase 3b study to assess the efficacy and safety of oseltamivir in immunocompromised subjects (adults and children ≥ 1 year old). Immunocompromised subjects were represented by solid organ transplant (SOT: liver, kidney, or liver and kidney) or hematopoietic stem cell transplantation (HSCT) recipients receiving once daily oseltamivir or placebo for 12 weeks. All subjects had to be negative at Baseline for a rapid diagnostic test for influenza virus.

The primary efficacy endpoint was the incidence of "standard" laboratory-confirmed clinical influenza, defined as:

- Fever (oral or otic temperature $> 37.2^{\circ}\text{C}$), and
- Symptom score on the diary cards of 1, 2 or 3 for cough and/or coryza on the same day, and
- Laboratory confirmation of influenza by either of the following:
 - Detection of viral shedding by viral culture from nasopharyngeal swabs within 2 days of fever or cough/coryza, and/or
 - Four-fold or greater increase in serum anti-HA antibody titers at any time during or after Tamiflu[®] treatment.

Although all swabs were tested by real-time RT-PCR for the presence of influenza virus matrix RNA, and only those samples that were RT-PCR positive were cultured, an RT-PCR positive sample was not considered laboratory positive for the primary efficacy endpoint unless it was also positive by quantitative culture. As requested by the FDA, a secondary efficacy endpoint using RT-PCR laboratory confirmation of influenza virus infection, rather than viral culture or ≥ 4 -fold increase in serum anti-HA antibody titers, was included in the study. Exploratory endpoints included analyses of oseltamivir treatment upon asymptomatic influenza infection (absence of fever) and an assessment of the predictive value of RT-PCR in the laboratory confirmation of influenza infection. Subject samples were archived for repeat analysis or for later analysis by improved methods.

Two nasal and one throat swab were collected from study participants during treatment on Days 7, 14, 28, 42, 56, 70, 84 (± 3), the follow-up visit on Day 112 (± 7), and during any illness visits (conducted when a subject developed influenza-like symptoms). Sera were collected from subjects at Baseline (Day 1, pre-dose), Day 56, and Day 112 for assay of anti-HA antibody titers. Subject serum and swab samples were transported to a central laboratory (ViroClinics) and assayed. Swabs were used to detect influenza A virus and influenza B virus matrix RNA by RT-PCR assay, and positive samples were then analyzed by quantitative virus culture on MDCK cells. Hemagglutinin

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inhibition assays (HAI) were performed with Baseline (Day 1), Day 56, and Day 112 subject sera using the following influenza virus strains: A/Solomon Island/3/2006 (H1N1), A/Wisconsin/62/2005 (H3N2), and B/Malaysia/2506/2004.

As detailed in the protocol, resistance analysis was limited to a comparison of viral isolates collected from the same subject at consecutive time points within the oseltamivir dosing period (i.e., from 3 days after the first dose of oseltamivir to 2 days after the last dose (Days 4-86)). The oseltamivir susceptibility of variants amplified by 1 passage on MDCK cultures would have been assessed using a fluorogenic substrate 2'-(4 methylumbelliferyl)- α -D-N-acetyneuraminic acid (MUNANA) based assay to assess neuraminidase activity. However, no oseltamivir-treated subjects met that criterion; thus, no resistance analysis was completed.

STUDY NV20236 was an open-label, multi-center, Phase 3b safety trial of oseltamivir for the seasonal prophylaxis of influenza in children 1 year to 12 years of age using daily dosing with 30-60 mg suspension (for children with body masses from ≤ 15 kg to 40 kg) or 75 mg suspension or capsules (for children with body masses > 40 kg). Although efficacy parameters (i.e., prevention of laboratory-confirmed clinical influenza) were assessed, no statistical analyses were performed because this was a single-arm study. The sponsor believed that historical comparison with data from previous prophylaxis studies would be acceptable for efficacy analyses.

Children were enrolled in the study if their primary care physician thought they would benefit from seasonal prophylaxis either because they were at risk of influenza virus infection or its complications, or they had the potential to infect other susceptible household members. All subjects had to be negative at Baseline for a rapid diagnostic test for influenza virus. Nasal and throat swabs were collected at Baseline and during illness visits (conducted when a subject developed influenza-like symptoms) and assessed for the presence of influenza virus by real-time RT-PCR and viral culture. This study excluded any child who had been vaccinated with live influenza virus (e.g., FluMist[®]) 2 weeks prior to enrollment because the concurrent use of oseltamivir with live influenza virus vaccine has not been evaluated, and there was a concern that oseltamivir might inhibit live vaccine virus replication and interfere with the development of an immune response to the virus.

The primary efficacy endpoint was the incidence of "standard" laboratory-confirmed clinical influenza, defined as:

- Symptoms of fever (oral/otic temperature $> 37.8^{\circ}\text{C}$), cough and coryza occurring on the same day while taking treatment, and
- Positive viral culture within 2 days of clinical symptoms, and/or
- $A \geq 4$ -fold rise in antibody titers at any point from baseline onward.

Additionally, exploratory analyses were to be conducted using:

- Laboratory-confirmed clinical influenza (defined as above) but with cough/coryza in the absence of fever
- Asymptomatic influenza, defined as an absence of fever and cough or coryza, but with laboratory-confirmed influenza.
- Influenza-like illness not caused by influenza virus. Defined as fever, cough and/or coryza on the same day without laboratory confirmation of clinical influenza.

4.1.1.2 Prior FDA Microbiological Reviews.

Prior Clinical Virology reviews relating to this supplemental NDA were conducted by Dr. N. Battula, Ph.D. for IND 053093 (SDN 298, 308, and 309), NDA 21087, and NDA 21246 and Dr. J. O'Rear for NDA 21087/21246 (SDN 374/245).

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4.1.1.3 Major microbiological issues that arose during product development

On November 5, 2009, DAVP recommended that the sponsor determine if the oseltamivir-resistance conferring substitution, NA H275Y, was present in influenza virus H1N1 RT-PCR positive samples or was known to be circulating at the location and time of the investigation. The sponsor agreed in a response sent on December 17, 2009 and included a summary of the reported incidence rates of H275Y-bearing strains of influenza A (H1N1) viruses at the time and regions of the study. On February 1, 2010 the sponsor submitted the results of genotypic testing specific for the H275Y substitution, and sent the results of their NA amino acid sequence analysis on February 18, 2010. The analyses indicated that prophylaxis failures could not be attributed to infection with a circulating oseltamivir-resistant variant or the selection of oseltamivir resistance during prophylaxis.. The communications and data are presented in Section 7, Clinical Virology.

4.2 State of antimicrobials used for the indication sought

Immunocompromised individuals may suffer more severe influenza virus infections and exhibit compromised responses to vaccination ([Goossen et al., 2009](#); [Kunisake and Janoff, 2009](#)). No drugs are currently approved for prophylaxis of influenza in immunocompromised subjects, (b) (4)

Oseltamivir is approved for prophylaxis of influenza in children ≥ 1 year old for a period of up to 10 days following exposure. However, seasonal prophylaxis for influenza typically requires 6 weeks of dosing to cover the period when influenza prevalence and risk for infection are highest. No drugs are currently approved for 6 weeks of prophylaxis in children.

5 Nonclinical Microbiology

5.1 Resistance Studies

No cell culture selection studies to characterize the genetic barrier to resistance, ascertain the genetic pathways to resistance, or determine cross-resistance to approved drugs were included in the application. For detailed analyses of prior resistance studies, see the Clinical Virology review conducted by Dr. N. Battula, Ph.D. for NDA 21087.

6 Relevant Findings from Other Disciplines.

6.1 Pharmacokinetics

No new pharmacokinetic data relevant to Clinical Virology were included in the application. For a detailed pharmacokinetic analysis, see the review by Dr. Huimin Zheng, Pharm.D.

6.2 Pharmacodynamics

No pharmacodynamic data relevant to Clinical Virology were included in the application. For a detailed pharmacodynamic analysis, see the review by Dr. Huimin Zheng, Pharm.D.

6.3 Clinical

The safety data suggest that both the 12-week administration of oseltamivir to transplant subjects and the 6-week treatment of children were well tolerated. For a detailed clinical safety analysis, see the review by Dr. Tafadzwa Vargasa-Kasambira, M.D., M.P.H.

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7 Clinical Virology

STUDY NV20235 was conducted from January 17, 2007 to June 3, 2008 in North America and Europe. A total of 475 persons were included in the ITT analysis for efficacy and resistance selection, 238 in the placebo arm and 237 in the oseltamivir arm. The primary efficacy endpoint was not met in the ITT population. The criteria for clinical influenza infection — which included laboratory confirmation by viral culture and/or seroconversion — were met by 7/238 (2.9%) in the placebo arm and 5/237 (2.1%) of the oseltamivir arm (Table 1), results that were insufficient to reject the null hypothesis ($p=0.77$). When defining clinical influenza virus infection solely by RT-PCR laboratory confirmation, the rate of infection in the placebo group remained unchanged at 2.9% (7/238) while that of the oseltamivir group was reduced to 0.8% (2/237). When addressing the disparity between the primary and secondary efficacy endpoints, the sponsor suggested that using seroconversion for laboratory confirmation may have led to 3 false positives. They reasoned that those subjects may have become infected after the oseltamivir-treatment period had ended, or suffered a delayed response to influenza vaccination as a result being immunocompromised. The study was also originally designed to demonstrate 80% protection using a sample size of 470 subjects (235 per arm) and assuming infection rates of 7.0% and 1.4% in the placebo and oseltamivir arms, respectively.

There were 12 subjects, 7 from the placebo group and 5 from the oseltamivir group, who were excluded from the ITTNAB population because they were real-time RT-PCR positive for influenza virus matrix RNA at baseline. Secondary efficacy analysis of the ITTNAB population demonstrated a 3.0% versus a 1.7% rate of infection between the placebo and oseltamivir arms, respectively (Table 1). When restricting the analysis to subjects with RT-PCR laboratory confirmation, the treatment effect was larger at 3.0% versus 0.4% for the placebo and oseltamivir arms, respectively.

TABLE 1 Summary of ITT and ITTNAB subjects with laboratory confirmed influenza virus infection, defined as fever ($>32.7^{\circ}\text{C}$) + symptoms (cough and coryza) + confirmation by one of two laboratory protocols

laboratory protocol	ITT				ITTNAB			
	Placebo		Oseltamivir		Placebo		Oseltamivir	
	#/238	%	#/237	%	#/231	%	#/232	%
"standard"	7	2.9%	5	2.1%	7	3.0%	4	1.7%
"RT-PCR"	7	2.9%	2	0.8%	7	3.0%	1	0.4%

"standard" = seroconversion or viral culture

"RT-PCR" = RT-PCR

There were 34 subjects who were positive for influenza virus matrix RNA by real-time RT-PCR for at least 1 time point during the study. Of those, 10 were positive outside of the dosing period (8 at baseline, and 2 after the dosing period). Of the 24 remaining ITTNAB real-time RT-PCR positive subjects, 20 were in the placebo arm and 4 in the oseltamivir arm (Table 2). Fourteen of the 24 were positive for influenza virus B and 10 for influenza virus A. Nine of the positive swabs from the placebo arm and 1 sample from the oseltamivir arm yielded virus cultures. Two subjects had culturable virus from more than 1 time point during the dosing period, but both were from the placebo arm (Table 2, highlights). One patient was infected with influenza A/H1N1 virus (Patient ID 87523/1547) and the other influenza B virus (Patient ID 87576/204). The isolates were sensitive to inhibition by oseltamivir, and, consistent with placebo treatment, no changes in susceptibility were observed (Table 3).

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TABLE 2. Subjects with laboratory confirmed influenza by RT-PCR during the dosing period of study NV20235

Treatment Arm	RT-PCR ⁺ Subject	Sample Day	Influenza	
			virus subtype	Titer (TCID ₅₀ /mL)
Placebo	87506/719	38	H1N1	0.75
	87515/7203	30	H3N2	≤0.5
		33	H3N2	≤0.5
	87516/6608	29	A-?	≤0.5
	87523/1514	1	H3N2	3.5
		8	H3N2	≤0.5
	87523/1544	42	B	4
		5	H1N1	2.75
		9	H1N1	3.25
	87523/1547	15	H1N1	3
		27	H1N1	≤0.5
	87524/1621	1	A-?	≤0.5
		7	H1N1	0.75
	87533/604	1	A-?	≤0.5
		57	B	3.75
	87547/3808	38	B	≤0.5
	87556/7602	16	H3N2	≤0.5
	87565/802	15	B	1.75
	87565/813	8	B	2
		16	B	≤0.5
	87571/7502	43	H1N1	≤0.5
		50	H1N1	≤0.5
		57	A-?	≤0.5
	87576/204	43	B	2.5
		45	B	2.5
		57	B	2.25
	87589/1324	28	B	≤0.5
	87611/6708	19	B	4.75
	87614/5765	29	A-?	≤0.5
	87614/5778	71	B	≤0.5
87624/3910	71	B	≤0.5	
87632/9304	28	B	≤0.5	
Oseltamivir	87506/716	7	H1N1	1.75
		14	A-?	≤0.5
	87524/1629	1	B	≤0.5
		8	B	≤0.5
	87591/8604	8	B	≤0.5
87632/9305	40	B	≤0.5	

Samples analyzed for oseltamivir susceptibility are highlighted; ≤0.5 denotes lack of detectable infection by MDCK culture; A-? denotes influenza A confirmation, but no subtype determination

TABLE 3 Comparing the oseltamivir susceptibilities in a neuraminidase assay of viral isolates collected at two different time points and to reference strains

Patient/Reference	Virus	IC ₅₀ value (nM)		Fold-change
		Time point #1	Time point #2	
Placebo 6	A/H1N1	2.2	3.8	1.45
Influenza A reference	A/Ned/306/00	1.2 [†]		
Placebo 14	B	76	49	0.64
Influenza B reference	B/Ned/022/95	20 [†]		

[†] IC₅₀ values for laboratory reference strains

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On November 5, 2009, DAVP communicated Virology comments to the sponsor, who sent a response on December 17, 2009 (SDN 396). The Division's comments are presented in bold and the sponsor's replies are italicized.

- 1. Please determine if the H275Y oseltamivir resistance-associated substitution is present in RT-PCR 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.

- 2. Please identify the clinical study site from which each RT-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 4] below. In addition, the incidence of oseltamivir-resistant influenza A (H1N1) is provided for samples that were influenza A/H1N1 or influenza A/unknown subtype.

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Table 4 Subjects with laboratory confirmed influenza by RT-PCR in study NV20235 - geographic region and incidence of oseltamivir-resistance

Pt. #	Study Arm	Type	Season ^a	Date of 1 st 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

Samples collected from 24 subjects during the dosing period were RT-PCR positive for influenza virus matrix RNA, 20 from the placebo-arm and 4 from the oseltamivir-treated group. Influenza viruses identified among the placebo-treated subjects included 4 influenza A/H1N1, 3 A/H3N2, 11 B, and 1 undetermined virus. The 4 viruses isolated from oseltamivir-treated patients included 1 influenza A/H1N1 and 3 influenza B viruses. According to the submitted data, the known incidences of oseltamivir-resistant influenza A H1N1 at the study sites was < 2%. Therefore, it was unlikely that influenza infection of oseltamivir-treated subjects was due to resistant variants.

On February 1, 2010 the sponsor submitted the results of additional genotypic testing.

There were 10 subjects who were either A/H1N1 or A/unknown PCR positive samples (8 placebo, 2 oseltamivir). Of these 10 subjects, there was a total of 5 subjects with nasal swab aliquots available with enough archived sample to test for the 275Y specific mutation. These 5 subjects had a total of 10 samples which were all analyzed for the resistance mutation. There were no culture supernatants available from any

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of these subjects to test. All of these 5 subjects were enrolled into the study in the 2007/08 influenza season within Israel and Hungary.

A central virology lab was utilized for the all sample testing for protocol NV20235. This same facility had stored sample aliquots of nasal swab material, and this lab was requested to perform the PCR assay for detection of the 275Y resistance tion.

Detection of H275Y mutation in NI NA by Real-Time PCR

Primers and probes (EuroGentec) are described below:

Primers and Probe for the Detection of seasonal 275H wild type and 275Y mutation:

Forward: 5' – aaaagggaaagggttactaaatcaatagagt -3'
Reverse: 5' – cagtgtctgggtaacaggaacatt -3'
Probe (wild type): 5' – caCcCaatTttCatTa -3'
Probe (275Y): 5' – caCcCaatTttTatTa -3'

Primers and Probe for the Detection of pandemic 275H wild type and 275Y mutation:

Forward: 5' – cagtcgaaatgaatgccctaa -3'
Reverse: 5' – tgcacacatgtgatttcatag -3'
Probe (wild type): 5' – ttaTCActAtgAggaatga -3'
Probe (275Y): 5' – ttaTTActAtgAggaatga -3'

Capital letters represent LNA bases. [LNA denotes locked nucleic acid, a modified RNA nucleotide that increases thermal stability of oligonucleotides].

Of the 10 samples tested for the 275Y specific mutation, 4 samples tested negative, all from the same subject. Four samples from 3 subjects resulted in no amplification of either the mutation or wild type, and two samples from 2 subjects were positive. Of the positive samples, one was from a subject with only 1 sample, the other positive subject had 2 samples, one positive and the other with no amplification.

Of the 2 subjects positive for the 275Y specific mutation, 1 was on placebo, and 1 on oseltamivir. These positive samples were taken on day 38 for the placebo subject, and day 7 for the oseltamivir subject. Both of these positive 275Y PCR samples originally tested positive by both PCR and culture on these days. The oseltamivir subject also tested PCR positive but not culture positive on day 14. This day 14 sample was not able to be subtyped, and this secondary testing showed no amplification. Both of these subjects tested negative for influenza by PCR and culture after repeated sampling during regularly scheduled study visits.

Both male subjects, ages 16 and 39, were from the same investigative site, and both completed the study. They each experienced mild upper respiratory tract infections [URTI] either before or at the time of the positive PCR samples. Both of these events were evaluated as mild, unrelated to study medication, and resolved without sequelae. The younger subject reported both mild cough, and fever of short duration in the symptom diary, but the event was not treated with any medication. The older subject was treated with a course of antibiotics, his adverse event was of a short duration [5 days] but did not report either symptoms or fever during the course of his URTI.

Samples which tested as Negative or No amplification for either mutation or wild type virus have been referred for full sequencing of the neuraminidase gene. Full results will be made available in the coming weeks

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Of the samples available for genotypic analysis, 4 tested negative, 4 failed to amplify by RT-PCR, and 2 were H275Y positive. Of the 2 positive samples, one was collected from a subject treated with placebo, and the other from an oseltamivir-treated subject. Data for the full NA sequence analysis was submitted on February 18, 2010 (Table 5).

Table 5 Neuraminidase amino acid sequence analysis of Influenza A H1N1 RT-PCR positive samples

Treatment Arm	RT-PCR ⁺ Subject	Sample Day	Influenza virus subtype	Neuraminidase Substitutions ¹						
				N104	S110	V114	A250	H275	D354	D386
Placebo	87506/719	38	H1N1	D ²	C ²	I	T	Y	G	G
		5	H1N1							
	87523/1547	7	H1N1							
		14	H1N1							
	87524/1621	28	H1N1	—	—	—	—	—	—	—
		1	A-?	—	—	—	—	—	—	—
	87533/604	7	H1N1	—	—	—	—	—	—	—
		1	A-?							
Oseltamivir	87506/716	7	H1N1					Y	G	
		14	A-?	—	—	—	—	—	—	—

¹ Influenza A (H1N1) A/Managua/4032.01/2008 was the reference strain

² Substitutions not present in the current public NCBI database of seasonal H1N1 amino acid sequences

³ " — " indicates that the amino acid sequence at this position could not be determined

⁴ A few amino acids near the C-terminus of NA were not determined by sequencing: position 470 for the Day 14 sample of patient 1547; positions 464-470 for the Day 7 sample of patient 1547 and samples of patient 719 and 716.

Although the 2 subjects infected by H275Y influenza variants were participants at the same investigative site in Jerusalem, Israel, differences in the NA amino acid sequences of their isolates suggest that they were infected by different strains, indicating selection of a resistant variant or transmission from another person treated with oseltamivir.

STUDY NV20236 was conducted from Dec. 18, 2006 to May 23, 2007. Although 52 children were enrolled and received an initial dose of oseltamivir, 3 children were not brought back for follow-up. Of the remaining 49 subjects who were included in the safety analysis population, 6 of these subjects (or their parents/guardians) withdrew consent during the study and did not complete the scheduled 6 weeks of dosing. Two additional subjects withdrew prematurely due to an AE. Thus, 41 subjects completed treatment and the 28 day follow-up. All subjects had a negative rapid diagnostic influenza virus test at baseline and 50/52 subjects had this confirmed by RT-PCR (2 subjects were not tested). Three subjects had received influenza vaccine within 6 months prior to enrollment (time since vaccination ranged between 27 and 82 days). There were no cases of clinical influenza virus infection, not even by RT-PCR laboratory confirmation, although serology results confirmed that 6 subjects did have at least a 4-fold increase in antibody titer.

No resistance data were generated for either NV20235 or NV20236. In Study NV20235, the protocol dictated that resistance analysis would be completed to compare the susceptibility of consecutive viral isolates cultured from the same subject. However, none of the samples collected from the oseltamivir-treated subjects yielded more than a single isolate. In Study NV20236, no laboratory confirmed clinical influenza infections were observed. Seasonal influenza virus with oseltamivir resistance was not known to have been circulating at the time these two studies were conducted.

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8 Conclusions

Although Studies NV20235 and NV20236 were useful for establishing safety under the experimental conditions, neither was able to demonstrate efficacy. [REDACTED] (b) (4)

9 Package Insert

In the last paragraph of the *Resistance* subsection of the product label, the sponsor proposed the following changes (changes are shown in red text):

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

The sponsor agreed to remove the last sentence from the label.

10 Recommendations

The amendments to the Tamiflu® labeling proposed by the applicant to include safety information related to the use of oseltamivir phosphate for 12-week prophylaxis in immunocompromised subjects and 6-week prophylaxis in pediatric subjects are acceptable.

11 References

- CDC. Oseltamivir-resistant novel influenza A (H1N1) virus infection in two immunosuppressed patients---Seattle, Washington, 2009. *MMWR*. Aug 21, 2009; 58(32):893-896.
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12 Appendix

12.1 Collection, receipt, and storage of human samples

ViroClinics received nasal and throat swab specimens directly from the study sites and were responsible for:

1. recovering swab eluates upon arrival;
2. dividing the eluate into specifically labeled aliquots using a barcode label
 - a. aliquot 1a: ~250 µL for real-time RT-PCR
 - b. aliquot 1b: ~600 µL for virus titration
 - c. aliquot 2: ~300 µL for virus genotyping
 - d. aliquot 3: ~250 µL for archiving
 - e. aliquot 4: ~500 µL for archiving
 - f. aliquot 5: ~300 µL for archiving
3. snap-freeze (dry-ice chips, with 96% ethanol) and storing all aliquots and culture supernatants at -80°C in specified boxes

The swab type used was the Aluminum Mini Swab and the manufacturer is Puritan Medical Products Co. LLC.

12.2 Detection of influenza A and B virus by real-time RT-PCR

1. Aliquot 1a is thawed at 37°C and 190 µL is mixed with 10 µL of internal control virus (phocine distemper virus)
2. RNA from aliquot 1a is isolated on the MagnaPure LC, an automated purification system based on the binding of nucleic acids to magnetic glass beads in the presence of chaotropic salt at pH > 7.
3. RNA isolated from aliquot 1a is used for the detection of influenza A and B virus matrix RNA in the TaqMan EZ Reverse Transcriptase real-time RT-PCR assay. Influenza A and B virus real-time RT-PCR specificity was confirmed using two reference strains from the National Influenza Centre: A/Brisbane/059/07 (Lot no. 0810A i2008-000334 (H1N1)) and B/Florida/004/06 (Lot no. 0811A). Samples positive for influenza A virus real-time RT-PCR were subtyped by real-time RT-PCR using influenza A virus H1 or H3 hemagglutinin-specific primers and probes (EuroGentec) presented in Table 6.
4. Results (POS, NEG, A, or B) are entered into the database NV20235

TABLE 6: Real-time RT-PCR primer sets and probes used for determining influenza virus genus and subtype

Influenza Genus Determination		
	Influenza A virus	Influenza B virus
Forward	5'-aagaccaatcctgtcacctctga	5'-gagacacaattgcctacctgctt
Reverse	5'-caaagcgtctacgctgcagtcc	5'-ttctttcccaccgaaccaac
Probe	5'-tttgtgttcacgctcaccgtgcc	5'-agaagatggagaaggcaaagcagaactagc
Influenza A Virus Subtype Determination		
	H1	H3
Forward	5'-gaatagccccactacaattgggtaa	5'-gatgtgtacagagatgaagcattaaaca
Reverse	5'-gtaattcgcattctgggtttcct	5'-taggatccaatcctttgatcctgactt
Probe(s)	5'-aagatccatccggcaacgctgca	5'-agctcaacacctttgatctggaaccgg 5'-agctcaacgcctttgatctggaaccgg

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12.3 Virus titration of positive influenza cultures

1. In cases where the TaqMan real-time RT-PCR for influenza A or B virus was positive, a virus titration assay was performed to culture influenza virus from the swab specimen
2. Aliquot 1b was thawed at 37°C
3. A virus titration assay was performed on MDCK cells by serially diluting aliquot 1b from 1:1 to 1:1,000,000 in cell medium on a 96 well tissue culture plate.
4. At 6 days post-infection, virus positive wells were identified by hemagglutination assay. Undiluted supernatants (25 µL) from each of the titration assay's wells were transferred to a 96 well round bottom plate, diluted with 50 µL of PBS, then 25 µL of 1% turkey erythrocytes added. Following an hour incubation at 4°C, hemagglutination patterns were read.
5. If a sample was culture positive, the supernatant was harvested and aliquoted as described below:
 - a. aliquot 6: for the neuraminidase enzyme phenotyping assay
 - b. aliquot 7: for archiving
6. The aliquots were snap-frozen prior to storage in a -80°C freezer. The aliquots were stored in the same box and registered in the sample tracking Excel file.
7. The virus titers were calculated by the Spearman/Karber method using the formula:
$$TCID_{50}/vol = X_0 - d/2 + d/n \sum X_i$$

Where:
 X_0 = positive logarithm of the highest dilution at which all quadruplicate wells are positive in the HA assay
 d = doses distance in log ($d = 1$ for these assays)
 n = number of repeats per dilution ($n = 4$ for these assays)
 $\sum X_i$ = the sum of all positive wells starting from X_0
8. Results are entered into the database NV20235
9. The limit of detection was reported to be ≤ 0.5 TCID₅₀/mL.

12.4 Influenza A virus subtyping

1. In cases where a swab specimen was positive for influenza A virus, a hemagglutinin-specific RT-PCR assay was performed to assess the subtype (H1- or H3-specific primers/probes)
2. Aliquot 3 was thawed at 37°C and 190 µL was mixed with 10 µL of internal control virus
3. RNA from aliquot 3 was isolated on the MagnaPure LC
4. Results (H1 or H3) were entered into the database NV20235

12.5 Validation of TaqMan real-time RT-PCR for the matrix influenza A and B virus RNA

Summary

Standard curves of the matrix influenza A and B virus Real-Time TaqMan assay were validated using two known influenza virus strains:

- A/Brisbane/059/07 Lot no. 0810A i2008-000334 (H1N1)
- B/Florida/004/06 Lot no. 0811A

These strains were obtained from the National Influenza Centre (NIC) and cultivated on MDCK (Madin-Darby Canine Kidney) Cells. The method of cultivation, harvesting and preparing the dilution series is described in: *Roche NV 20234B Influenza A/B Real-Time PCR: Validation proposal Influenza A and B standard curves*. Standard curves were generated and compared with the TCID₅₀ values of both strains.

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The specificities of the influenza A and B virus primer/probe sets were demonstrated by running dilution series of the influenza A virus standard curve against the influenza B virus primer/probes. The dilution series of the influenza B virus standard curve was also run against the influenza A virus primer/probes.

Acceptance criteria: All results must be negative.

The linearity was tested by running the dilution series of each reference sample in triplicate on the TaqMan 7500. Standard curves were made and the slopes determined.

Reproducibility and repeatability were demonstrated by running the standard curves of each virus strain in triplicate over a period of 5 days by two technicians performing one run each, per day.

Acceptance criteria: Assay values are considered qualified when triplicate measurements are within one C_t cycle of the mean. Standard deviations of repeatability should be within the set margin of two cycles of the mean.

All requirements were met for the validation of the Roche NV20234B influenza A/B Real-Time PCR influenza A and B virus standard curves.

During the Roche NV20234B study 3 points (low, middle and high) of both influenza A and B virus standard curves will be used as controls and will accompany every TaqMan run.

Materials

Isolation and purification of nucleic acids

- MagNA Pure LC Total Nucleic Acid Isolation Kit, cat. no: 3038505, Roche Applied Science
- MagNA Pure LC Processing Cartridge, cat. no: 3004147, Roche Applied Science
- MagNA Pure LC Sample Cartridge, cat.no:3004112, Roche Applied Science
- MagNA Pure LC Reagent Tub (large), cat.no:3004040, Roche Applied Science
- MagNA Pure LC Reagent Tub (small), cat.no:3004066, Roche Applied Science
- MagNA Pure LC Tip Stand, cat. no: 3004155, Roche Applied Science
- MagNA Pure LC Reaction Tip (large), cat. no: 3004171, Roche Applied Science

Amplification assays

- TaqMan® EZ RT-PCR PCR Core Reagents, cat. no: N8080236, Applied Biosystems (lot no. K08377, Exp date: 31-jul-2009)
- DEPC (Diethyl pyrocarbonate), cat. no: D5758, Sigma-Aldrich
- MicroAmp™ Optical Adhesive Film, cat. no: 4311971, Applied Biosystems
- MicroAmp™ Optical 96-Well Reaction Plate, cat. no: N8010560, Applied Biosystems
- MicroAmp™ Adhesive Film Applicator, cat. no: 4333183, Applied Biosystems
- MicroAmp™ 96-Well Support Base, cat. no: 4379590, Applied Biosystems
- PDV primer/probe, Erasmus Medical Centre, batch 11 date: 17-Dec-2008
- Influenza A Primer/Probe, Erasmus Medical Centre, batch 17 date: 11-Aug-2008
- Influenza B Primer/Probe, Erasmus Medical Centre, batch 8 date: 30-Aug-2008

Samples

- Internal control: PDV, clinical isolate, Erasmus Medical Centre

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- A/Brisbane/059/07 Lot no. 0810A i2008-000334 (H1N1, NIC); B/Florida/004/06 Lot no. 0811A (NIC); both strains are clinical isolates that were propagated on MDCK-cell cultures. Samples were obtained from the National Influenza Centre. Methods are described in the Roche NV 20234B Influenza A/B Real-Time PCR: Validation proposal Influenza A and B virus standard curves.

Equipment

- MagNA Pure LC Instrument, cat. no: 2236931, Roche Applied Science (equipment no: VC-140)
- MagNA Pure LC Instrument, cat. no: 2236931, Roche Applied Science (equipment no: VC-0233)
- Real-Time PCR System, cat. no: 4351105, Applied Biosystems (equipment no: VC-0275)
- Real-Time PCR System, cat. no: 4351105, Applied Biosystems (equipment no: VC-0276)
- Freezer -20°C and -80°C
- Refrigerator $+4^{\circ}\text{C}$
- Biosafety Cabinet/Flow cabinet
- Monochannel precision micropipettes (5 μl -1000 μl)
- Multichannel precision micropipettes (20 μl -200 μl)
- Sterile filter tips
- Pipet boy
- Disposable pipet (5mL)
- Vortex
- Gloves

Methods

Nucleic acids were isolated using the MagNA Pure LC Isolation station and the Total Nucleic Acid isolation kit (Roche Applied Science)..

The amplification and detection was performed with a Real-Time RT-PCR System (Applied Biosystems)

Results

Specificity of the influenza A and B virus primer/probes were demonstrated by running the dilution series of the influenza A virus standard curve against the influenza B virus primer/probes. The dilution series of the influenza B virus standard curve was also run against the influenza A virus primer/probes. Three isolations of each strain were examined.

Acceptance criteria: All results must be negative. The acceptance criteria were met.

Linearity was tested by making dilution series of the virus strains. Samples were run in triplicate on the TaqMan 7500, a standard curve was made, and the slope was determined. During the validation a total of 33 standard curves were produced.

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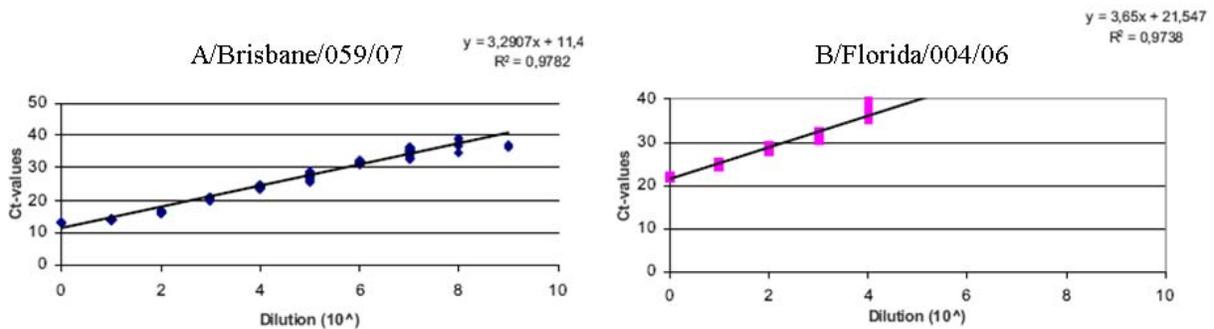


FIGURE 1: Standard curves illustrating the relationship between C_t value and the amount of input RNA

The TCID₅₀ values were determined for both influenza A and B virus strains. The TCID₅₀ values were:

Influenza A virus TCID₅₀/100μL: 7.00

Influenza B virus TCID₅₀/100μL: 1.50

Reproducibility and repeatability were demonstrated by running the standard curve of each virus strain in triplicate over a period of 5 days by two technicians.

Acceptance criteria: Assay values were considered qualified for repeatability when triplicate measurements were within one C_t cycle of the mean with standard deviations of two cycles. In total, 33 standard curves were run for both influenza A and B virus. The acceptance criteria were met.

Controls

Internal Control - Phocine Distemper virus (PDV; a paramyxovirus)

The PDV internal control gives information about the nucleic acid extraction. This control contained the appropriate PCR mix and PDV RNA template.

Acceptance criteria: Results will be accepted when the C_t values of the PDV lies between 24.92 and 28.56. In a few samples the PDV was out of range. After repeating the TaqMan PDV run of these samples, the acceptance criteria were met.

No amplification controls (NACs)

NACs give information about possible contamination during nucleic acid extraction. This control contained the appropriate PCR mix supplemented with the nucleic acid extraction control instead of viral template.

Acceptance criteria: All NACs must be positive in the PDV run and negative in the discrimination assay. All NACs were positive in the PDV run and negative in the matrix PCR. The acceptance criteria were met.

No template controls (NTCs)

NTCs give information about possible contamination in the PCR reagents. This control contained the appropriate PCR mix supplemented with elution buffer from the isolation kit, instead of viral template. For each PCR run at least one NTC was included.

Acceptance criteria: All NTCs must be negative. All NTC were negative. The acceptance criteria were met.

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Conclusions

All requirements were met for the validation of the Standard curves used for Real Time TaqMan influenza A/B virus Matrix PCR:

During the study, a 3-point (high, middle and low) standard curve was included with each TaqMan run. Based on the results of the validation of the standard curves the following dilutions are chosen:

Influenza A virus: 10^{-2} mean C_t value: 16

10^{-4} mean C_t value: 24

10^{-6} mean C_t value: 32

Influenza B virus: 10^{-1} mean C_t value: 25

10^{-2} mean C_t value: 28

10^{-3} mean C_t value: 32

Interestingly, the real-time RT-PCR assay was not used quantitatively. On January 29, 2010 DAVP requested information regarding the sponsor's use of RT-PCR:

Was the TaqMan EZ RT-PCR the assay used to determine if a swab sample was influenza positive? If so, was the influenza RNA load also quantified as stated in the protocol? Was the same assay then used to determine influenza A subtype?

*Yes, the TaqMan EZ RT-PCR assay was used to determine if the swab sample was positive with the influenza matrix PCR. This is a semi-quantitative assay system. Performance parameters are described in the enclosed Report RPT-VAL-160-RCH-FLuAB-FNL (**Attachment 4**). The EZ kit was also used for subtyping with subtype specific PCR. Assay performance parameters are described in reports RPT-VAL-FluAH1-SND and RPT-VAL-FluAH3-SND, which are enclosed (**Attachments 5 and 6**).*

Although the submitted documents demonstrated that the assay was reproducible, there was no report demonstrating the limit of detection; nor were there data that demonstrated that the primer/probe sets were specific for strains of influenza virus circulating at the time and locations of the study.

12.6 Neuraminidase enzyme phenotyping assay

1. If virus titration of a swab specimen was positive for influenza, a neuraminidase enzyme phenotyping assay was performed using material collected at the time of the first and last positive cultures.
2. Aliquot 6 was thawed at 37°C
3. The NA enzyme phenotyping assay was performed.
4. Results (IC_{50} values) were entered into the database NV20235

12.6.1 Neuraminidase Phenotyping (Research report: W142966 and NDA 21087/21246 SDN 374/245, response to Clinical Virology request for information, reviewed by Dr. Julian J. O'Rear, Ph.D.)

In response to a Clinical Virology request for susceptibility data communicated to the sponsor by email on July 7, 2009, the sponsor stated:

There are two standard assays that have been used for determining oseltamivir sensitivity phenotype with clinical samples, a fluorescent assay based on MUNANA substrate and a luminescent assay (NA-star). Both assays have been widely used for global surveillance of community isolates and in clinical studies. The global Neuraminidase Inhibitor Susceptibility Network (NISN) has been established in 1999 to standardize the assays

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for global use, to provide guidance for phenotyping assay performance and to publish summary results from global phenotyping activities. Typical EC₅₀ values and ranges for laboratory strains and clinical isolates using these assays have been published in cooperation with the NISN group ([Wetherall et al., 2003](#), *J Clin Microbiol.*; [McKimm-Breschkin et al., 2003](#), *Antimicrob. Agents Chemother.*; [Monto et al., 2006](#), *Antimicrob. Agents Chemother.*). In addition, a reference panel of virus strains has been established by NISN to standardize global phenotyping activities (http://www.nisn.org/virus_reference_panel.html). Mean EC₅₀ values and ranges differ slightly between these two assay formats based on slight differences in substrate binding affinity and concentration, as oseltamivir is a competitive inhibitor of neuraminidase activity (see Table 6 below).

TABLE 6. Influenza neuraminidase IC₅₀ values

Assay	Isolate #	NISN analysis (Wetherall et al. 2003 J. Clin. Microbiol.)						NISN reference panel (http://www.nisn.org/)		
		H1N1		H3N2		B		H1N1	H3N2	B
		Mean EC50 (SD) [nM]	EC50 range [nM]	Mean EC50 (SD) [nM]	EC50 range [nM]	Mean EC50 (SD) [nM]	EC50 range [nM]			
Fluorescent assay	1	3.42 (0.81)	2.19-4.17	1.60 (0.25)	1.25-1.85	65.75 (19.01)	44.40-96.80	0.6 - 3.0 ^a	0.2 - 0.8 ^a	In progress
	2	6.78 (5.79)	1.96-16.90	0.96 (0.13)	0.75-1.11	71.05 (23.02)	45.90-114.00			
	3	3.70 (1.44)	1.38-5.27	1.05 (0.20)	0.77-1.25	88.87 (12.48)	68.10-104.00			
	4	2.79 (1.43)	0.81-5.21	0.75 (0.16)	0.59-0.99	64.32 (19.98)	41.00-94.90			
Luminescent assay	1	0.48 (0.17)	0.36-0.98	0.54 (0.16)	0.32-0.90	3.99 (0.85)	2.89-5.80	0.7 (0.2) ^b	0.4 (0.1) ^b	In progress
	2	0.47 (0.13)	0.37-0.82	0.52 (0.14)	0.41-0.94	3.63 (0.73)	2.86-5.57			
	3	0.47 (0.09)	0.36-0.64	0.37 (0.07)	0.25-0.53	4.81 (1.75)	2.99-9.35			
	4	0.43 (0.10)	0.29-0.65	0.41 (0.03)	0.37-0.48	5.32 (2.46)	0.54-8.75			
	5	0.40 (0.29)	0.01-1.05	0.30 (0.10)	0.22-0.59	3.58 (0.59)	2.55-4.53			

^a EC₅₀ range [nM]; ^b Mean EC₅₀ value (SD)

Materials

MUNANA-based fluorescence assay:

- 2-(4-methylumbelliferyl)-a-D-N-acetylneuraminic acid (MUNANA) (Sigma #M8639)
- 2-[N-morpholino]ethanesulphonic acid (MES) (free acid) (Sigma #M8250)
- 1M Calcium Chloride (CaCl₂) (BDH # 19046 4K)
- Surfactant-Amps-NP-40 (10% solution) (Pierce #28324)
- Bovine Serum Albumin (50mg/mL, protease free) (Gibco BRL #15561-020)
- 0.824M and 10M Sodium Hydroxide (NaOH(aq))
- Neuraminidase Inhibitor GS 4071 (RO 64-0802/000) (BN 1163.85.36)
- Positive Control Virus (A/Victoria H3N2 and A/WS H1N1 (Gilead Sciences, USA). Received as 5 mL tissue culture supernatant and Split into 5µL aliquots and frozen at -70°C
- MicroAmp Optical 96 well Reaction Plate (PE Applied Biosystems #N801-0560)
- MicroAmp Full Plate Cover (PE Applied Biosystems #N801-0550)
- Cytoplate NS (PerSeptive Biosystems CFC PN 9650)
- Microplate Cover (Labsystems # 9503157)
- GeneAmp PCR System 9700 Thermal Cycler (96-well) (PE Applied Biosystems)
- Stat Fax 220 Plate Incubator/Shaker (Awareness Technology Inc.)
- Cytofluor 2350 Fluorescence Measurement System (Millipore)

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
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NDA: 21087 SE-049/21246 SE-035 SDN 378 DATE REVIEWED: 1/25/10

Luminescence Assay:

- 2-(4-methylumbelliferyl)-a-D-N-acetylneuraminic acid (MUNANA) (Sigma #M8639)
- 2-[N-morpholino]ethanesulphonic acid (MES) (free acid) (Sigma #M8250)
- 1M Calcium Chloride (CaCl₂) (BDH # 19046 4K)
- Surfactant-Amps-NP-40 (10% solution) (Pierce #28324)
- Bovine Serum Albumin (50mg/mL, protease free) (Gibco BRL #15561-020)
- 0.824M and 10M Sodium Hydroxide (NaOH(aq))
- Neuraminidase Inhibitor GS 4071 (RO 64-0802/000) (BN 1163.85.36)
- Positive Control Virus (A/Victoria H3N2 and A/WS H1N1 (Gilead Sciences, USA).
- MicroAmp Optical 96 well Reaction Plate (PE Applied Biosystems #N801-0560)
- MicroAmp Full Plate Cover (PE Applied Biosystems #N801-0550)
- Microfluor white flat bottom plate (VWR#62402-980)
- PTC-100 Programmable Thermal Controller (96-well) (M J Research)
- Luminescence Spectrometer LS 50B (Perkin Elmer)

Methods

Solutions and cultures

For the MUNANA-based fluorescence assay, oseltamivir was prepared at concentrations of 0.03, 0.3, 3, 30, 300, 3000 and 30000 nM in 2XAB, which corresponded to 0.01, 0.1, 1, 10, 100, 1000, and 10000 nM in the final assay volume. For the luminescence assay, oseltamivir was prepared at concentrations of 0.03, 0.3, 3, 30, 300, and 3000 nM, which corresponded to concentrations of 0.01, 0.1, 1, 10, 100, and 1000 nM in the final assay volume.

The MUNANA substrate was prepared as a 5 mM stock prepared by addition of 10 mL distilled water to 25 mg MUNANA. The stock solution was stored in 800 µL aliquots at -20°C.

The 0.824M sodium hydroxide was prepared by adding 32.96 g of NaOH (s) to 1 L distilled water.

5 mL of each positive control virus culture supernatants was aliquoted in a Biological Safety Cabinet as follows:

9 X 0.5 mL aliquots (sterile)

100 X 5 µL aliquots (non-sterile)

Aliquots were frozen at -80°C

Storage of clinical samples

Clinical samples were initially sent to Erasmus University, Rotterdam or ViroMED Laboratories, Minneapolis. First and last day virus positive samples were then expanded for one round of replication in monkey kidney cells.

Two aliquots for each first and last day positive samples were then shipped on dry ice from Erasmus and ViroMED to Roche Discovery Welwyn and Gilead Sciences respectively. On receipt, sample numbers were checked against a list sent in advance from Erasmus or ViroMED. Sample numbers and date received were recorded on a spreadsheet. Samples were then organized into a reference set and a working set. These were stored at -70°C.

Samples from the working set were tested in the assay. Once a sample had been tested, it was split into two aliquots (one aliquot was retained in the original tube, the other was placed in an eppendorf tube clearly labeled

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with the sample number). This gave two 'working sets' which were stored in separate -70°C freezers. Samples were split in order to minimize freeze-thawing, should repeat testing be required.

Assay Preparations

Preparation of Working Strength Substrate

For 1 plate: 720 μ L 5 mM MUNANA added to 5.28 mL 1XAB

Preparation of Stop Solution

Both methods give 0.14M NaOH in 83% ethanol.

Fluorescence assay

For 1 plate: 2.225 mL 0.824M NaOH added to 11 mL ethanol

Stop solution was prepared fresh for each experiment due to precipitation problems.

Luminescence assay

For 1 plate: 175 μ L 10M NaOH + 1.95 mL water added to 10.375 mL ethanol

Stop solution was prepared fresh for each experiment due to precipitation problems

Preparation of Positive Control Samples

Positive control samples were prepared in a Biological Safety Cabinet. Positive control viruses were tested at 1/100 dilution in 1XAB. NP-40 and BSA were added to give 0.1% and 0.3 mg/mL, respectively, in the final volume (500 μ L):

5 μ L virus stock

5 μ L 10% NP-40

3 μ L 50 mg/mL BSA

487 μ L 1XAB

To avoid spiking small quantities of BSA and NP-40 into samples, a bulk of NP-40, BSA and 1XAB was prepared prior to use:

30 μ L 10% NP-40

18 μ L 50 mg/mL BSA

2.922 mL 1XAB

495 μ L of the above was then added to each tube containing 5 μ L positive control virus. Samples were left to stand for 5 minutes.

Addition of NP-40 rendered the virus non-infectious and subsequent assay steps did not require the use of a Biological Safety Cabinet. BSA was added to samples to minimize non-specific binding in the assay. Samples were vortex mixed prior to testing.

Preparation of Clinical Samples

Clinical samples were prepared in a similar manner to the positive control samples. Samples were mixed then diluted as required in 1XAB. Samples were tested at 1/10 initially then repeated at a higher or lower dilution if necessary. NP-40 and BSA were added to give 0.1% and 0.3 mg/mL respectively in the final volume (500 μ L). A bulk of BSA, NP-40 and 1XAB was prepared prior to use:

5.89 mL 1xAB

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67 µL 10% NP-40
40 µL 50 mg/mL BSA

450 µL of the above was then added to 50 µL clinical sample in a Biological Safety Cabinet. Samples were left to stand for 5 minutes to inactivate virus. Samples were vortex mixed prior to testing.

Assay Procedure

Assays were performed using a thermal cycler or a plate incubator.

Thermal cycler method:

1. 50 µL clinical sample or control was added to the MicroAmp plate. 50 µL 1XAB was added for the no virus well.
2. A dummy plate containing inhibitor dilutions ranging from 0 (1XAB only) to 30,000 nM oseltamivir as prepared. 50 µL inhibitor was then added to each test well using a multichannel pipette.
3. The plate was incubated on the instrument for 45 minutes at 25°C.
4. 50 µL working strength substrate was next added to the plate using a multichannel pipette.
5. The plate was incubated on the instrument for 2 hours at 37°C.
6. The plate was cooled to 4°C then the reaction stopped by addition of 100 µL stop solution.
7. 220 µL was next taken from each well (using a multichannel pipette) and placed in a cytoplate.
8. The plate was read using the following parameters:

	Wavelength (nm)	Slit Width (nm)
Excitation	360	2.5
Emission	448	20

Plate incubator method:

1. The plate incubator method was adapted from the thermal cycler method. Each plate incubator had the capacity to run two plates simultaneously and was more economical in terms of equipment costs. Throughput was thus increased to four plates per assay run.
2. 50 µL clinical sample or control was added to a cytoplate. 50 µL 1XAB was added for the no virus well.
3. A dummy plate containing inhibitor dilutions ranging from 0 (1XAB only) to 30,000 nM of oseltamivir was prepared. 50 µL inhibitor was then added to each well using a multichannel pipette.
4. The plate was incubated on the bench with a lid for 45 minutes.
5. 50 µL working strength substrate was next added to the plate using a multichannel pipette.
6. The plate was incubated in the plate incubator for 2 hours at 37°C.
7. The reaction was next stopped by addition of 100 µL stop solution.
8. The plate was read using the following parameters:

	Wavelength (nm)	Slit Width (nm)
Excitation	360	2.5
Emission	448	20

Results

Fluorescence-based assay:

Microsoft Excel was used for the processing of results.

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1. Background fluorescence (average counts for the no virus wells) was calculated then subtracted from the counts of each well.
2. For each sample or control, results from inhibited wells were calculated as a percentage of the uninhibited fluorescence.
3. Results were then plotted as % uninhibited activity versus inhibitor concentration (nM) on a semi-log plot. Inhibitor concentration was expressed as 0 to 10,000 nM. First and last positive samples were plotted on the same graph.
4. A logistic curve fit program written by Dr. T. Rae (IS, Welwyn) was used to produce a curve of best fit for each sample. This program calculated the IC₅₀ value for each curve using the following equation:

$$f(x) = \frac{(Max - Min)}{\left(1 + \left(\frac{x}{x_{infect}}\right)^{Grad}\right)^{Symmetry}} + Min$$

Where:

Max = asymptotic maximum
 Min = asymptotic minimum
 x = independent variable
 x_{infect} = point of inflection
 Grad = gradient
 symmetry = symmetry factor

5. The IC₅₀ values for the first and last samples were then compared. A significant increase in the IC₅₀ value was suggestive of a resistant variant.

Luminescence-based assay:

Sigma Plot was used to process the results.

1. Background luminescence (average counts for the no virus wells) was calculated then subtracted from the counts of each well.
2. For each sample or control, results from inhibited wells were calculated as a percentage of the uninhibited luminescence.
3. Results were then plotted as % uninhibited activity versus inhibitor concentration (nM) on a semi-log plot. Inhibitor concentration was expressed as 0 to 1,000 nM. First and last positive samples were plotted on the same graph.
4. Sigma Plot was used to solve the following equation:

$$f(x) = \left(\frac{IC_{50}^n}{IC_{50}^n + x^n}\right) \times 100$$

Where:

f(x) = % uninhibited activity
 x = inhibitor concentration
 n = Hill's coefficient

5. The IC₅₀ values for the first and last samples were then compared. A significant increase in the IC₅₀ value was suggestive of a resistant variant.

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NDA: 21087 SE-049/21246 SE-035 SDN 378 DATE REVIEWED: 1/25/10

12.7 Genotyping

1. In cases where the IC₅₀ values from variants isolated from consecutive samples from one subject showed significant changes, a genotypic analysis of the genes for HA and NA was performed
2. Aliquot 2 was thawed at 37°C
3. A genotypic analysis of the gene for NA was performed by Sanger sequencing using the Big Dye terminator sequencing kit version 3.0 (Amersham Pharmacia Biotech) and a 3100 genetic analyzer (Applied Biosystems).
4. The NA sequence of influenza A/Managua/4032.01/2008 (H1N1) was used as a reference sequence.
5. All human H1N1 NA protein sequences available by February 5, 2010 that were at least 100 amino acids long were used in the polymorphism analysis.

12.8 Hemagglutination inhibition assay

1. ViroClinics received and recorded serum specimens directly from the study sites. Upon arrival, serum was stored at -20°C.
2. All sera from subjects was be tested for the presence of antibodies directed against the most recent and available H1N1, H3N2, and influenza B strains in the HAI assay
3. Sera was thawed at 37°C
4. HAI was performed with the following influenza virus strains:
 - a. A/Solomon Island/3/2006 (H1N1)
 - b. A/Wisconsin/67/2005 (H3N2)
 - c. B/Malaysia/2506/2004
5. A 1:2 serial dilution of sample sera (the final serum concentration for the first dilution was 1:20) was mixed with one of the test influenza strains and incubated at 37°C for 30 minutes. One-half volume of 1% turkey erythrocytes were added to each well and incubated at 4°C for 1 hour. Wells were then scored for inhibition of hemagglutination and titers determined:

Score	Inhibition of agglutination	Corresponding titers
0	Not present	<10
++	Half at dilution 1:20	10
1	Complete at dilution 1:20	20
1++	Half at dilution 1:40	30
2	Complete at dilution 1:40	40
2++	Half at dilution 1:80	60
3	Complete at dilution 1:80	80
3++	Half at dilution 1:160	120
4	Complete at dilution 1:160	160
4++	Half at dilution 1:320	240
5	Complete at dilution 1:320	320
5++	Half at dilution 1:640	480
6	Complete at dilution 1:640	640
6++	Half at dilution 1:1280	960
7	Complete at dilution 1:1280	1280
7++	Half at dilution 1:2560	1920
8	Complete at dilution 1:2560	2560
8++	Half at dilution 1:5120	3840
9	Complete at dilution 1:5120	5120
9++	Half at dilution 1:10240	7680
10	Complete at dilution 1:10240	10240
10++	Half at dilution 1:20480	15360
11	Complete at dilution 1:20480	20480 or higher

6. Results were entered into the database NV20235

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21087	SUPPL-49	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES

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/s/

DAMON J DEMING
02/26/2010

JULIAN J O'REAR
02/26/2010

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW**

NDA: 21087 SE-049/21246 SE-035 SDN 403 DATE REVIEWED: 01/27/10

Reviewer: Damon J. Deming, Ph.D.

Date Submitted: 01/15/10

Date Assigned: 01/26/10

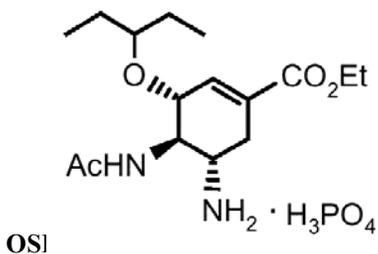
Date Received: 01/19/10

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-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester, phosphate

Structure:



Molecular formula: C₁₆H₂₈N₂O₄ (free base)

Molecular weight: 312.4 for the free base, 410.4 for the phosphate salt

Drug category: Antiviral

Indication: [REDACTED] (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 403 DATE REVIEWED: 01/27/10

BACKGROUND and SUMMARY

This submission consists of the sponsor's reply to a non-Clinical Virology request to justify the exclusion of subjects with positive serology endpoints plus clinical symptoms from the efficacy analysis. This response is of interest to Virology because it might represent a shift in the sponsor's opinion of the value of RT-PCR as an indication of clinically-relevant influenza infection. The Agency's request is **bolded** and the sponsor's reply is *italicized*.

Please provide additional justification for excluding subjects with positive serology endpoint plus clinical symptoms from the efficacy analysis. We agree that subjects who have been recently transplanted may not respond to an immunologic challenge but for subjects further out from transplant a 4-fold rise in antibody titer in conjunction with ILI [influenza like illness] symptoms may represent an appropriate response.

This study included the immunocompromised population defined as either liver and/or kidney transplants, or hematopoietic stem cell transplants. The primary endpoint was chosen based on the historic endpoints for the registration studies, i.e. using culture, and/or a 4-fold rise in antibody titer to indicate the presence of influenza infection. PCR testing was added at the request of the health authorities who wanted to ensure the detection of patients who have a low viral burden.

Immune response in immunocompromised subjects is not clear, as results of several studies addressing this issue have reported different outcomes. Vaccine-induced serum antibody responses were impaired severely in solid tumor transplant recipients in some studies, but in other studies the response was similar to those in healthy controls ([Soesman et al., 2000](#)). Thus, there is no clear evidence that this patient population has a consistent, and measurable antibody response due to their immune suppression.

In study NV20235, a full 1/3rd of the study participants in each arm showed a 4-fold increase in antibody titer only on day 112. This was 28 days past the last dose of study medication, and could have been from exposure to influenza virus after treatment.

PCR relies on direct detection of virus, does not rely on viable virus, and has been accepted as the method of choice for early diagnosis of acute influenza ([Allwinn et al., 2002](#)). Further, CDC has published an interim guidance on their website which states real-time RT-PCR is the recommended test for confirmation of novel influenza A (H1N1) cases (<http://www.cdc.gov/h1n1flu/specimencollection.htm>). Serology can only be used to diagnose suspected influenza retrospectively, requires acute and convalescent titers, and may not be reflective of current practice.

CONCLUSIONS

We agree that RT-PCR is the preferred method for confirming influenza infection, and we will continue to encourage the sponsor to use RT-PCR in their future clinical trials. There are no comments to be communicated to the sponsor.

**DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
MICROBIOLOGY REVIEW**

NDA: 21087 SE-049/21246 SE-035 SDN 403 DATE REVIEWED: 01/27/10

Damon J. Deming, Ph.D.
Clinical Microbiology Reviewer

CONCURRENCES:

_____ Date _____
HFD-530/J. O'Rear /TL Micro

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21087	SUPPL-49	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES

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/s/

DAMON J DEMING
01/27/2010

JULIAN J O'REAR
01/27/2010

VIROLOGY FILING CHECKLIST FOR NDA or Supplement

NDA Number: 21087

Applicant: Hoffman-LaRoche Inc. **Stamp Date:** 09/12/2009

Drug Name: oseltamivir

NDA Type: Priority

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the virology information (nonclinical and clinical) provided and described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the virology information (nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		
3	Is the virology information (nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant <u>submitted</u> cell culture data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?			Not applicable
5	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?			Not applicable
6	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	X		
7	Has the applicant <u>submitted</u> the clinical virology datasets in the appropriate format as described in the relevant guidance documents and are the datasets complete?	X		NV20235: <ul style="list-style-type: none"> • Some virology data • No resistance data NV20236: <ul style="list-style-type: none"> • No virology data
8	Has the applicant used standardized or nonstandardized methods for virologic outcome measures? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	X		
9	Has the applicant <u>submitted</u> draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
10	Has the applicant <u>submitted</u> annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	X		

VIROLOGY FILING CHECKLIST FOR NDA or Supplement

	Content Parameter	Yes	No	Comments
11	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?	X		
12	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? YES

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Not to be communicated to the sponsor:

The sponsor added text to the last paragraph of the Microbiology/Resistance section in the product label (new additions in red text):

In clinical studies of postexposure and seasonal prophylaxis in immunocompetent persons, 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)

We are going to ask for the removal of the last sentence. It is misleading given that (b) (4)

Reviewing Microbiologist

Date

Microbiology Team Leader

Date

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/s/

DAMON J DEMING
09/24/2009

JULIAN J O'REAR
09/25/2009

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021087/S-049

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

IND	53,093 (S-407)
Submission Date	January 12, 2009
Brand Name	Tamiflu
Generic Name	Oseltamivir
Primary Reviewer	Sarah Robertson, PharmD
Secondary Reviewer	Kellie Reynolds, PharmD
OCP Division	DCP 4
OND Division	DAVP
Formulation; Strength	75 mg capsules and 12 mg/mL suspension
Indication	Treatment and prophylaxis of influenza

1. EXECUTIVE SUMMARY

Study WP21272 was a drug-drug interaction study conducted to evaluate the effect of oseltamivir coadministration on warfarin pharmacokinetics and pharmacodynamics. The results of the study indicate that oseltamivir does not have an effect on warfarin pharmacokinetics when oseltamivir is given at a dose of 75 mg BID for 5 days to subjects stabilized on warfarin therapy. Further, there were no marked differences in the pharmacodynamics of warfarin (INR, Factor VIIa activity and plasma concentrations of vitamin K₁) during coadministration with oseltamivir. Compared to historical control data collected in younger healthy volunteers, oseltamivir and oseltamivir carboxylate exposures were greater in this warfarin-maintained study population. However, subjects in the current study were older and had a history of cardiovascular-related illness, which likely impacted the observed differences in this cross-study comparison. Warfarin would not be expected to impact either the conversion of oseltamivir to the carboxylate metabolite, nor the renal excretion of oseltamivir carboxylate. The results of the study confirm that oseltamivir and warfarin can be safely coadministered with no need for increased monitoring of warfarin therapy.

Questions were raised regarding a potential interaction between oseltamivir and warfarin during the 2009 influenza season, based on reports of spontaneous INR increases in patients with influenza receiving oseltamivir while on warfarin therapy. In addressing this concern, Roche reported to the FDA on August 20, 2009 (SDN-385) the company's ongoing post-marketing safety review did not support an interaction between oseltamivir and warfarin, consistent with the results of Study WP21272.

The INR increases observed in patients on warfarin therapy concomitantly with oseltamivir may be due to influenza rather than the oseltamivir. Literature reports indicate the production of interferon (IFN) and other inflammatory mediators in response to viral and bacterial infection results in the inactivation of CYP450 enzymes.¹⁻³ One of the first indications that infection can evoke changes in drug metabolism was a case series of 11 asthmatic children who developed a sudden increase in theophylline concentrations with related toxicity during an influenza outbreak.⁴ Since this original report, others have reported on influenza-related changes in theophylline clearance and an increased risk of associated toxicity. It is hypothesized that influenza-mediated release of IFN inhibits CYP1A2-mediated theophylline metabolism. CYP450 enzymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2 and 3A4, though 2C9 is the principal enzyme responsible for the metabolism of *S*-warfarin. The *S*-enantiomer has 2-5 times more anticoagulant activity than *R*-warfarin. It appears that various inflammatory mediators and cytokines cause differential effects on the different CYP450 enzymes, with certain mediators more potent modulators of specific enzymes than others.

Several cytokines have demonstrated downregulation of CYP2C activity, including IL-1, IL-6 and tumor necrosis factor (TNF).^{5,6} It is hypothesized that inflammatory mediators released during acute influenza infection result in downregulation of warfarin metabolism, thereby increasing INR and potentially leading to an increased risk of bleeding events. Spontaneous INR increases in patients receiving oseltamivir for treatment of influenza while on warfarin therapy are unlikely to be the result of a drug interaction, but rather may be due to downregulation of warfarin metabolism by influenza-related inflammatory mediators.

An efficacy supplement was submitted to the Tamiflu NDA on August 7, 2009 (21-087, S-049) to expand the prophylaxis indication to pediatric patients 1 to 12 years of age and to immunocompromised patients ≥ 1 year of age. The supplement also includes a conversion of the label to PLR format. No new clinical pharmacology data were submitted with the supplement. In order to address concern about a potential interaction, warfarin should be added to the list of drugs in the label that oseltamivir does not interact with, based on the results of Study W21272.

2. RECOMMENDATION

The following revision to the product label is recommended:

7 DRUG INTERACTIONS

No pharmacokinetic interactions have been observed when coadministering oseltamivir with amoxicillin, acetaminophen, cimetidine, (b)(4)-antacids (magnesium and aluminum hydroxides and calcium carbonates), or warfarin.

3. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Study WP21272 was an open-label, randomized, 2-period crossover study to investigate the PK, PD and safety of warfarin and oseltamivir coadministration in subjects stabilized on warfarin therapy. The study was conducted in England between February 8, 2008 and July 10, 2008. Subjects were male or female, between 18-75 years of age (inclusive), stabilized on a warfarin dose for ≥ 4 weeks with an INR between 2.0-3.5, a BMI 18-32 kg/m², no recent use of any prohibited medications, including probenecid and inducers or inhibitors of CYP450 (unless stabilized on the medication for ≥ 3 months concomitantly with warfarin), and a CrCl ≥ 60 mL/min.

There were two treatment periods of 5 days duration each, separated by a ≥ 4 day washout period. Subjects were randomized to the order in which the two treatments were received.

Treatment A: Subject receives their usual once daily maintenance dose (and brand) of warfarin.

Treatment B: Subject receives their usual once daily maintenance dose (and brand) of warfarin, plus oseltamivir 75 mg BID for 4 days, with a single dose on Day 5. Oseltamivir was administered with food.

Serial PK samples were collected on Days 1, 4 and 5 for evaluation of plasma concentrations of R- and S-warfarin, oseltamivir (parent) and oseltamivir carboxylate (active metabolite). Pharmacodynamic evaluations included assessments of INR, Factor VIIa activity and plasma

concentrations of vitamin K₁. Subjects were admitted to the study unit for both treatment periods and remained on site until Day 6.

Twenty warfarin-maintained subjects were enrolled in the study and completed participation. Maintenance doses of warfarin ranged from an average of 0.5 mg to 9 mg/day. Some of the subjects did not receive the same warfarin dose each day of the week (e.g. 2 mg on Mon/Wed/Fri and 3 mg on Tues/Thurs/Sat/Sun). As such, some subjects may have received a different dose on the same PK sampling day of the different treatment periods.

Plasma samples were analyzed for oseltamivir and oseltamivir carboxylate using a validated LC/MS/MS method. Samples were also analyzed for free and total *R*- and *S*-warfarin by a validated LC/MS/MS method. The performance characteristics of both assays were acceptable, with estimates of accuracy and precision and calibration curve parameters falling within predetermined acceptability limits, and appropriate use of quality control standards.

Warfarin AUC and C_{max} values were dose-normalized by the individual average dose (D_{avg}) over the 5 days of treatment to account for differences in dose. In general, variability in *R*- and *S*-warfarin PK parameters was high, even after adjusting for dose (Table 1). However, there were no significant differences in the exposure of either enantiomer when given with or without oseltamivir (Table 2).

Table 1. Summary of Mean (SD) PK Parameters of *R*- and *S*-Warfarin by Treatment

	(S)-warfarin				(R)-warfarin			
	Total		Free		Total		Free	
	A (N=20)	B (N=20)	A (N=20)	B (N=20)	A (N=20)	B (N=20)	A (N=20)	B (N=20)
Primary								
C _{max} /D _{avg} (ng/mL/mg) (± SD)	394 (±259)	330 (±197)	1.87 (±1.30)	1.68 (±1.13)	436 (±243)	375 (±96.3)	2.70 (±1.45)	2.37 (±0.604)
AUC _{0-24h} /D _{avg} (h*ng/mL/mg) (± SD)	6770 (±4500)	6460 (±4310)	35.2 (±26.1)	33.9 (±24.1)	7790 (±2480)	7360 (±1960)	49.4 (± 13.4)	48.3 (±11.9)
Secondary								
AUC _{0-12h} /D _{avg} (h*ng/mL/mg) (± SD)	3610 (±2200)	3380 (±2100)	18.6 (±13.0)	17.8 (±12.3)	4140 (±1320)	3870 (±1020)	25.9 (±7.84)	24.8 (±6.36)
t _{max} ^a (h) (range)	2.00 (1.00– 8.13)	4.00 (0.00– 23.92)	14.5 (8.74– 53.8)	3.01 (1.00– 8.00)	3.00 (1.00– 11.83)	4.00 (1.00– 23.92)	4.00 (1.00– 11.83)	3.00 (1.00– 11.83)
t _{1/2} (h) (± SD)	45.4 ^c (±23.0)	45.6 ^d (±11.7)	NC	NC	56.1 ^b (±26.1)	53.6 ^b (±12.2)	NC	NC
CL/F (L/h) (± SD)	0.198 (±0.0895)	0.208 (±0.0959)	38.5 (±17)	38.2 (±15.1)	0.139 (±0.0361)	0.145 (±0.0374)	21.7 (±5.74)	22 (±5.54)

^a As an exception t_{max} is expressed as a median (range)

^b N=12; ^c N=13; ^d N=11

Note: Whenever N <10, i.e. more than 50% of the data is missing, the mean was not calculated (NC)

Table 2. Summary Statistical Analysis for the Effect of Oseltamivir on Warfarin

--Warfarin+Oseltamivir vs Warfarin Alone--
--Least Square Means---

Analyte	Parameter	Warfarin Alone	Warfarin+ Oseltamivir	Ratio*	90% CI
Free S Warfarin	AUC(0-24) (ng.hr/mL)	87.17	85.72	0.98	(0.95, 1.02)
	C _{max} (ng/mL)	4.56	4.21	0.92	(0.85, 1.01)
Total S Warfarin	AUC(0-24) (ng.hr/mL)	10466.87	9996.33	0.96	(0.90, 1.01)
	C _{max} (ng/mL)	603.47	528.66	0.88	(0.78, 0.99)
Free R Warfarin	AUC(0-24) (ng.hr/mL)	87.17	85.72	0.98	(0.95, 1.02)
	C _{max} (ng/mL)	4.56	4.21	0.92	(0.85, 1.01)
Total R Warfarin	AUC(0-24) (ng.hr/mL)	13662.39	13005.66	0.95	(0.90, 1.01)
	C _{max} (ng/mL)	728.37	664.17	0.91	(0.83, 1.00)

Single dose and steady-state PK parameters of oseltamivir and oseltamivir carboxylate were compared to results from a Phase 2 study conducted in healthy young volunteers experimentally infected with influenza B (NP15717) (Table 3). Exposure of both the parent drug and the active carboxylate metabolite were greater in the current study relative to the former Phase 2 study on Day 1 and at steady-state. However, the differences in exposure are likely due to the cross-study comparison and differences in subject populations. Of note, subjects in the current study were older, with a mean age of 62 (range 47 – 75). Although baseline creatinine clearance values are not reported, this older group of warfarin-maintained subjects likely had less efficient renal clearance due to a history of cardiovascular-related disease. Oseltamivir is converted to the carboxylate metabolite by esterases in the liver, prior to elimination by renal excretion. Warfarin would not be expected to impact either the conversion of the parent to the carboxylate metabolite, nor the renal excretion of oseltamivir carboxylate.

Table 3. Summary of Mean (SD) PK Parameters of Oseltamivir (Ro 64-0796) and Oseltamivir Carboxylate (Ro 64-0802)

	Single Dose (Day 1)				Steady State (Day 5)			
	Ro 64-0796		Ro 64-0802		Ro 64-0796		Ro 64-0802	
	WP21272 (N=20)	NP15717 (N=20)	WP21272 (N=20)	NP15717 (N=20)	WP21272 (N=20)	NP15717 (N=20)	WP21272 (N=20)	NP15717 (N=20)
Primary parameters								
C _{max} (ng/mL)	88.9	62.9	367	225	91.2	65.2	571	348
(± SD)	(±50.0)	(± 31.5)	(±107)	(± 48.9)	(±47.2)	(± 16.7)	(±160)	(± 63.6)
AUC _{0-12h} (h*ng/mL)	141	99.6	2990	1607	169	112	5110	2719
(± SD)	(±38.3)	(±24.2)	(±793)	(± 325)	(±36.3)	(± 27.5)	(±1630)	(± 539)
Secondary parameters								
AUC _{0-24h} (h*ng/mL)	-	-	-	-	176	NR	7180	NR
(± SD)					(±38.5)		(±2550)	
t _{max} (h) ^a	0.50		4.00		0.75		4.00	
(range)	(0.50– 3.00)	NR	(2.00– 6.00)	NR	(0.50– 3.00)	NR	(3.00– 6.00)	NR
t _{1/2} (h) ^b	1.77	1.36	6.17	5.49	4.00	2.18	8.19	5.79
(± SD)	(±0.686)	(± 0.430)	(±2.07)	(± 1.44)	(±3.08)	(± 0.991)	(±1.90)	(± 1.25)
CL/F (L/h)	558	774	-	-	463	708	-	-
(± SD)	(±134)	(± 247)			(±104)	(± 182)		

Note: Oseltamivir was only administered (and PK samples taken) in one treatment period (Treatment B)

NR = Not reported

^a As an exception t_{max} is expressed as a median (range)

^b t_{1/2} is 'apparent' for the active metabolite (Ro 64-0802)

There were no significant changes in INR during coadministration of warfarin with oseltamivir in Treatment B. Mean Area Under the Plasma Effect-Time Curve (AUEC) values from Days 1-5 were -2.2 and -9.0 for Treatments A and B, respectively (Table 4). Mean maximum absolute change in INR was 0.3 and 0.1 for Treatments A and B, respectively. There were two outliers with sporadic increases in INR during Treatment A (warfarin alone) and one outlier with a marked decrease in INR while receiving Treatment B (warfarin + oseltamivir) (Figure 1). In the exploratory repeated measures analysis, there was no statistically significant effect of treatment or day of INR measurement on INR change-from-baseline, but there was a significant period effect, with a greater reduction from baseline in Period 1 vs. Period 2.

Table 4. Summary of INR Changes by Treatment Group

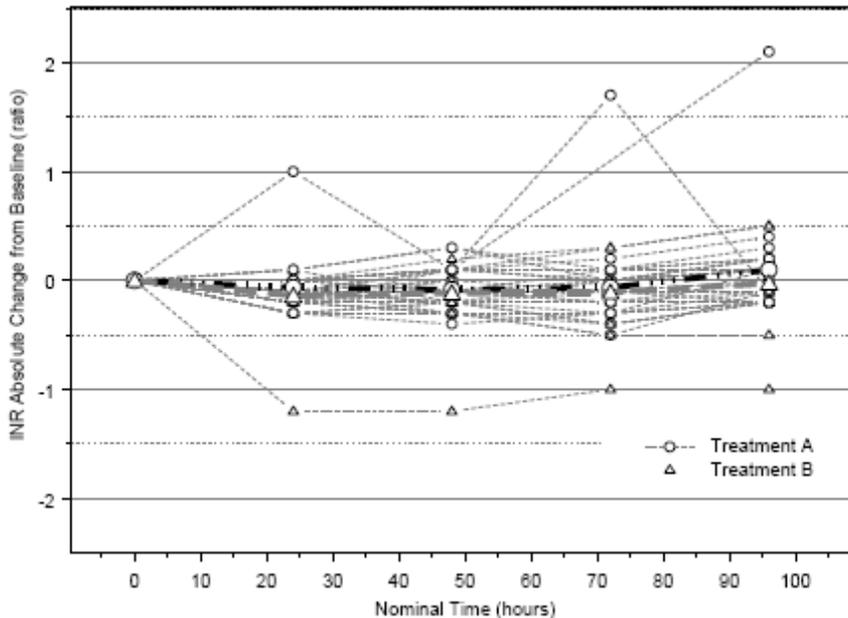
	Primary parameters				Secondary parameter	
	AUEC _{0-96h} [Net] (h*ratio)		E _{max} [Abs. Change] (ratio)		T _{max} * (h)	
	A	B	A	B	A	B
N	20	20	20	20	20	20
Mean	-2.16	-9.06	0.3	0.1	24.00	0.00
Range	(-27.6-78.0)	(-93.6-18.0)	(0.0-2.1)	(0.0-0.5)	(0.00-96.00)	(0.00-96.00)

A: Warfarin alone o.d. p.o. (subject's usual dosing regimen)

B: Warfarin o.d. p.o. + oseltamivir 75 mg b.i.d. p.o. for 4 days with a single dose on Day 5

* As an exception T_{max} is expressed as a median

Figure 1. Change in INR from Baseline (Days 1-5) by Treatment



Treatment A: Warfarin Alone o.d. p.o. (subject's usual dosing regimen)

Treatment B: Warfarin o.d. p.o. + oseltamivir 75 mg b.i.d. p.o. for 4 days with a single dose on Day 5

Note: Overlaid mean plots are provided for both treatments: Treatment A (thick black line with round markers) and Treatment B (thick grey line with triangular markers)

The Factor VIIa pharmacodynamic parameters (AUEC_{0-96h} and E_{min}) were similar between treatments. The mean results were 0.568 and 1.45 for AUEC_{0-96h} and -0.05 and -0.04 for E_{min} for Treatments A and B, respectively. There was a trend for increased Vitamin K₁ plasma concentrations over the 5 days of study treatment in both treatment groups, but no observable difference between the two groups. Mean (range) change in Vitamin K₁ concentrations were 305 (-371 – 1060) ng/L and 271 (-1100 – 1310) ng/L following Treatments A and B, respectively.

Conclusion

The results of the study indicate that oseltamivir does not have an effect on warfarin PK or PD when oseltamivir is given at a dose of 75 mg BID for 5 days to subjects stabilized on warfarin therapy. Compared to historical control data collected in younger healthy volunteers, oseltamivir and oseltamivir carboxylate exposure were greater in this warfarin-maintained study population. However, subjects in the current study were older and had a history of cardiovascular-related illness, which likely impacted the observed differences of this cross-study comparison. Warfarin would not be expected to impact either the conversion of oseltamivir to the carboxylate metabolite, nor the renal excretion of oseltamivir carboxylate. The results of this study confirm that oseltamivir and warfarin can be safely coadministered with no need for increased monitoring of warfarin therapy.

4. REFERENCES

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-53093	ORIG-1	HOFFMANN LA ROCHE INC	GS-4104-02 ORAL CAPSULES
NDA-21087	SUPPL-49	HOFFMANN LA ROCHE INC	TAMIFLU 75 MG CAPSULES

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/s/

SARAH M ROBERTSON
01/19/2010

KELLIE S REYNOLDS
01/19/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021087/S-049

OTHER REVIEW(S)

MEMORANDUM

To: Robert Kosko
Division of Antiviral Products

From: Iris Masucci, PharmD, BCPS
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: February 5, 2010

Re: Comments on draft labeling for Tamiflu (oseltamivir phosphate)
NDA 21-087/S-049
NDA 21-246/S-035

We have reviewed the proposed label for Tamiflu (FDA version received by SEALD 2/4/10) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21087	SUPPL-49	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/

IRIS P MASUCCI
03/11/2010

LAURIE B BURKE
03/16/2010

**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, (b) (4) was changed to (b) (4)
5. Throughout the label, (b) (4) was changed to (b) (4)
6. The last two columns in Tables 1 and 2 were renamed as follows:

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

Number of TAMIFLU Capsules (b) (4) to Dispense (b) (4)
 (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] (b) (4) was removed from the end of Section 2.3 **Standard Prophylaxis of Influenza**.
10. Section 2.4 [REDACTED] (b) (4) was renamed to **Renal Impairment**.
11. The [REDACTED] (b) (4) 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] (b) (4) plasma concentrations of oseltamivir carboxylate [REDACTED] (b) (4) 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] (b) (4) continuous peritoneal dialysis treatment [REDACTED] (b) (4).

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] (b) (4) statement under section 2.7 **Preparation of TAMIFLU for Oral Suspension** was deleted [REDACTED] (b) (4)

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

The constituted TAMIFLU for oral suspension (b) (4) (12 mg/mL) should be used within 17 (b) (4) 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 <u>Patient</u> (b) (4) (mL)
≤15 kg	≤33 lbs	30 mL
<u>>15</u> (b) (4) to 23 kg	<u>>33</u> (b) (4) to 51 lbs	40 mL
<u>>23</u> (b) (4) to 40 kg	<u>>51</u> (b) (4) to 88 lbs	50 mL
<u>>40</u> (b) (4) kg	<u>>88</u> (b) (4) 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 (b) (4) 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 (b) (4) -one-third (1/3) of the total (b) (4) -amount of vehicle in 3 small portions to (b) (4) -the mortar while triturating with the pestle (b) (4) 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 (b) (4) -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) (b) (4) -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 (b) (4)-inert ingredients of TAMIFLU capsules (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 (b) (4)-that any unused suspension remaining in the bottle (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 (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 $\geq 1\%$ 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 $\geq 1\%$ 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 [REDACTED] (b) (4)

[REDACTED] -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:

[REDACTED] (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 [REDACTED] (b) (4) -Multiple Dosing of 75 mg Capsules Twice Daily [REDACTED] (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 (AUC_{0-24h}) 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 $>99.0^{\circ}\text{F}/37.2^{\circ}\text{C}$ plus cough and/or coryza, all recorded within 24 hours, plus either a positive virus

culture (b) (4) or a four-fold increase in virus antibody titers from baseline. The (b) (4) incidence of (b) (4) confirmed clinical influenza was (b) (4) 3% (7/238) in the group not receiving TAMIFLU compared with (b) (4) 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. (b) (4)

—Among subjects who were not already shedding virus at baseline, (b) (4) the incidence of RT-PCR (b) (4) confirmed clinical influenza was (b) (4) 3% (7/231) in the group not receiving TAMIFLU and (b) (4) <1% (1/232) in the group receiving TAMIFLU. (b) (4)

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 (b) (4) 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

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 021087/S-049

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-087 and 21-246

SUPPL # 049 and 035

HFD # 530

Trade Name Tamiflu®

Generic Name oseltamivir phosphate

Applicant Name Roche Laboratories, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1), SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Safety and activity of oseltamivir for 12 weeks as seasonal prophylaxis of influenza in immunocompromised patients 1 year of age and older and the safety of oseltamivir for 6 weeks as seasonal prophylaxis of influenza in pediatric patients between 1 and 12 years of age.

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-087 Tamiflu ® (oseltamivir phosphate) Oral Capsules, Approved October 27, 1999
NDA # 21-246 Tamiflu ® (oseltamivir phosphate) for Oral Suspension, Approved December 14, 2000

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

- 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"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

- 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"

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 53,093

YES

!
!

! NO

! Explain:

Investigation #2

IND # 53,093

YES

!
!

! NO

! Explain:

Title: Deputy Director, Division of Antiviral Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

DEBRA B BIRNKRANT
02/22/2010



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

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

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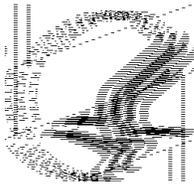
DATE: February 18, 2010

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

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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
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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**

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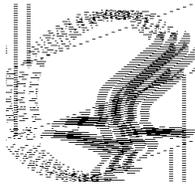
DATE: January 29, 2010

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 NDA 21-246/S-035: Comment for 8-7-09 Submission	

Total no. of pages including cover: 4

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-087/S-049 and 21-246/S-035
Drug: Tamiflu (oseltamivir phosphate)
Date: January 29, 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: Comment for 8-7-09 Submission

Please refer to your submission dated August 7, 2009. We have the following comments:

Please provide detailed methodologies for the following procedures and assays used in Studies NV20235 and NV20236. The SOP number(s) is provided when it was referenced in the submission:

1. Swab type and manufacturer; area of sampling
2. Virus propagation and titration on cell culture (VC-M003). Please provide the diagnostic and quantitative viral culture performance characteristics for strains of influenza that were circulating at the time the studies were conducted.
3. Isolation of RNA from clinical sample (SOP VIR-A127)
4. All RT-PCR assays. The assays' performance parameters for influenza strains that were circulating at the time of the clinical studies are of particular interest.
 - a. Was the TaqMan EZ RT-PCR the assay used to determine if a swab sample was influenza positive? If so, was the influenza RNA load also quantified as stated in the protocol? Was the same assay then used to determine influenza A subtype?
5. Genotypic analysis (VIR-M330)
6. Hemagglutinin inhibition assay (VC-M005)

Please respond to these comments within 1 week.

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
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/s/

Robert G Kosko
01/29/2010



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Office of Antimicrobial Products**

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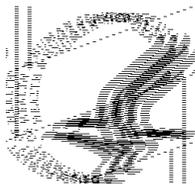
DATE: January 25, 2010

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: 22

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

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

Drug: Tamiflu (oseltamivir phosphate) Capsules and Oral Suspension

Date: January 25, 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 January 25, 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

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/s/

Robert G Kosko
01/25/2010



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

FACSIMILE TRANSMITTAL SHEET

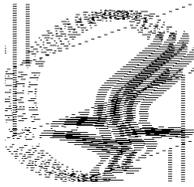
DATE: January 6, 2010

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 NDA 21-246/S-035: Comment for 12-17-09 Submission	

Total no. of pages including cover: 3

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-087/S-049 and 21-246/S-035
Drug: Tamiflu (oseltamivir phosphate)
Date: January 6, 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: Comment for 12-17-09 Submission

Please refer to your submission dated December 17, 2009. We have the following comment:

1. We agree to your proposal for resistance testing as outlined in the submission.

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-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
01/06/2010



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

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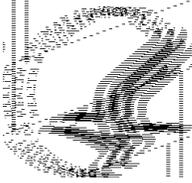
DATE: December 11, 2009

To: S. Elizabeth Lucini, Pharm.D. Program Manager, Drug Regulatory Affairs	From: Elizabeth Thompson, M.S. 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)796-0824
Subject: Tamiflu efficacy supplements (S-049/S-035): request for information	

Total no. of pages including cover: 2

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

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

Drug: Tamiflu (oseltamivir phosphate)

Date: December 11, 2009

Sponsor: Hoffmann-La Roche, Inc.

From: Elizabeth Thompson, Regulatory Project Manager

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

Subject: Tamiflu efficacy supplements (S-049/S-035): request for information

Please refer to NDA 21087/S-049 and 21246/S-035 submitted August 7, 2009. We have the following requests for information.

1. Please provide additional justification for excluding subjects with positive serology endpoint plus clinical symptoms from the efficacy analysis. We agree that subjects who have been recently transplanted may not respond to an immunologic challenge but for subjects further out from transplant a 4-fold rise in antibody titer in conjunction with ILI symptoms may represent an appropriate response.

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

ELIZABETH G THOMPSON
12/11/2009



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

FILING COMMUNICATION

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

Dear Dr. Lucini:

Please refer to your August 7, 2009 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TAMIFLU (oseltamivir phosphate) capsules and oral suspension.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, this supplemental application is considered filed 60 days after the date we received your supplemental application in accordance with 21 CFR 314.101(a). The review classification for this supplemental application is **Priority**. Therefore, the user fee goal date is February 10, 2010.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 11, 2009.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

NDA 21-087/S-049

NDA 21-246/S-035

Page 2

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

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.

Director

Division of Antiviral Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

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

DEBRA B BIRNKRANT
10/02/2009



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

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-049
21-246/S-035

Date of supplement: AUGUST 7, 2009

Date of receipt: AUGUST 10, 2009

This supplemental application proposes 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"

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 OCTOBER 10, 2009 in accordance with 21 CFR 314.101(a).

NDA 21-087/S-049

NDA 21-246/S-035

Page 2

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, M.S., Regulatory Project Manager, at (301) 796-0824.

Sincerely,

{See appended electronic signature page}

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

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

ELIZABETH G THOMPSON
09/10/2009