CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21246/S-017

Trade Name: **TAMIFLU**

Generic Name: **Oseltamivir Phosphate**

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

Approval Date: 12/21/2005

Indications: TAMIFLU is indicated for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21246/S-017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21246/S-017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-246/S-017
NDA 21-087/S-030

Hoffman-La Roche Inc.
Attn: Karen Noh, Senor Program Manager, Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms. Noh:

Please refer to your supplemental new drug applications dated April 15, 2005, received April 18, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tamiflu® (oseltamivir phosphate) Oral Suspension and Capsules.

We acknowledge receipt of your submissions to NDA 21-246 dated June 10, 2005, August 8, 2005, August 29, 2005, and November 30, 2005, and your December 16, 2005 submission to both NDAs.

These supplemental new drug applications provide for the use of Tamiflu (oseltamivir phosphate) Oral Suspension and Capsules for prophylaxis of influenza for patients between 1-12 years of age.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert and patient package insert submitted December 16, 2005).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplements NDA 21-246/S-017 and NDA 21-087/S-030.**" Approval of the submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application for ages 1-12, and we waive the pediatric study requirement for birth to less than one year of age.

We remind you of your postmarketing study commitment in your submission dated December 16, 2005. This commitment is listed below.

1. Collect and submit safety data in a population of 40-50 pediatric patients 1 to 12 years of age using the approved prophylaxis dosing recommendations for a period of up to 6 weeks in the setting of seasonal influenza prophylaxis. Evaluation of "influenza high risk" patient groups is suggested.

Protocol Submission:	by December, 2006
Study Start:	by 2006-2007 influenza season
Final Report Submission:	by July, 2008

Submit final study reports to these NDAs. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly 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

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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 Jeff D. O'Neill, Regulatory Health Project Manager, at (301) 796-0777.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products

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

/s/

Debra Birnkrant
12/21/2005 01:16:50 PM
NDA 21-246, 21-087

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21246/S-017

LABELING

TAMIFLU®

(oseltamivir phosphate)

CAPSULES

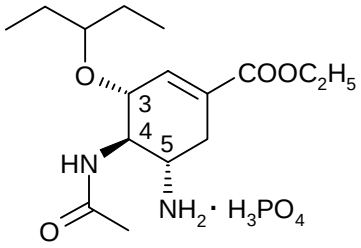
AND FOR ORAL SUSPENSION

R_X only

DESCRIPTION

TAMIFLU (oseltamivir phosphate) is available as a capsule containing 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 K 30, croscarmellose sodium, and sodium stearyl fumarate. The 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 xanthan gum, monosodium citrate, sodium benzoate, sorbitol, saccharin sodium, titanium dioxide, and tutti-frutti flavoring.

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:



MICROBIOLOGY

Mechanism of Action

Oseltamivir is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate. The proposed mechanism of action of oseltamivir is inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

Antiviral Activity In Vitro

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% inhibitory concentrations (IC_{50} and IC_{90}) were in the range of 0.0008 μM to >35 μM and 0.004 μM to >100 μM, respectively (1 μM=0.284 μg/mL). The relationship between the in vitro 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 in vitro by passage of virus 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 mutations selected in vitro in neuraminidase are I222T and H274Y in influenza A N1 and I222T and R292K in influenza A N2. Mutations E119V, R292K and R305Q have been selected in avian influenza A neuraminidase N9. Mutations A28T and R124M have been selected in the hemagglutinin of influenza A H3N2 and mutation 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 vitro to oseltamivir carboxylate. Mutations in influenza A 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, determination of resistance 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 vitro. 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 mutations (E119V, H274Y and R292K) in the viral neuraminidase from clinical isolates occur at the same amino acid residues as two of the three mutations (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.

CLINICAL PHARMACOLOGY

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 1**).

Table 1 Mean (% CV) Pharmacokinetic Parameters of Oseltamivir and Oseltamivir Carboxylate After a Multiple 75 mg Capsule Twice Daily Oral Dose (n=20)

Parameter	Oseltamivir	Oseltamivir Carboxylate
C_{max} (ng/mL)	65.2 (26)	348 (18)
$AUC_{0\text{-}12h}$ (ng·h/mL)	112 (25)	2719 (20)

Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily (see **DOSAGE AND ADMINISTRATION**).

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 abnormal renal function administered various dose regimens of oseltamivir are described in **Table 2**.

Table 2 Oseltamivir Carboxylate Exposures in Patients With Normal and Reduced Serum Creatinine Clearance

Parameter	**Normal Renal Function**			**Impaired Renal Function**				
	75 mg qd	75 mg bid	150 mg bid	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.

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: Special Dosage Instructions**).

INDICATIONS AND USAGE

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.

Prophylaxis of Influenza

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

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

Description of Clinical Studies: Studies in Naturally Occurring Influenza

Treatment of Influenza

Adult Patients

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

Of 1355 patients enrolled in these two trials, 849 (63%) patients were influenza-infected (age range 18 to 65 years; median age 34 years; 52% male; 90% Caucasian; 31% smokers). Of the 849 influenza-infected patients, 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 Patients

Three double-blind placebo-controlled treatment trials were conducted in patients ≥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 patients enrolled, 476 (65%) patients were influenza-infected. Of the 476 influenza-infected patients, 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 Patients

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

Prophylaxis of Influenza

Adult Patients

The efficacy of TAMIFLU in preventing naturally occurring influenza illness has been demonstrated in three seasonal prophylaxis studies and a postexposure prophylaxis study in households. The primary efficacy parameter for all these studies was the incidence of laboratory-confirmed clinical influenza. Laboratory-confirmed clinical influenza was defined as oral temperature ≥99.0ºF/37.2ºC plus at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one constitutional symptom (aches and pain, fatigue, headache, chills/sweats), all recorded within 24 hours, plus either a positive virus isolation or a fourfold 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 4.8% (25/519) for the placebo group to 1.2% (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 4.4% (12/272) for the placebo group to 0.4% (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 Patients

The efficacy of TAMIFLU in preventing naturally occurring influenza illness has been demonstrated in a randomized, open-label, postexposure prophylaxis study in households that included children aged 1 to 12 years, both as index cases and as family contacts. All index cases in this study received treatment. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the household. Laboratory-confirmed clinical influenza was defined as oral temperature ≥100°F/37.8°C plus cough and/or coryza recorded within 48 hours, plus either a positive virus isolation or a fourfold 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 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.

CONTRAINDICATIONS

TAMIFLU is contraindicated in patients with known hypersensitivity to any of the components of the product.

PRECAUTIONS

General

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

Use of TAMIFLU should not affect the evaluation of individuals for annual influenza vaccination in accordance with guidelines of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.

Efficacy of TAMIFLU in patients who begin treatment after 40 hours of symptoms has not been established.

Efficacy of TAMIFLU in the treatment of subjects 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.

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

Efficacy of TAMIFLU for treatment or prophylaxis has not been established in immunocompromised patients.

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.

Hepatic Impairment

The safety and pharmacokinetics in patients with hepatic impairment have not been evaluated.

Renal Impairment

Dose adjustment is recommended for patients with a serum creatinine clearance <30 mL/min (see **DOSAGE AND ADMINISTRATION**).

Serious Skin/Hypersensitivity Reactions

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

Information for Patients

Patients should be instructed 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.

Patients should be instructed 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.

Drug Interactions

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.

Cimetidine, a non-specific inhibitor of cytochrome P450 isoforms and competitor for renal tubular secretion of basic or cationic drugs, has no effect on plasma levels of oseltamivir or oseltamivir carboxylate.

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.

Coadministration with amoxicillin does not alter plasma levels of either compound, indicating that competition for the anionic secretion pathway is weak.

In six subjects, multiple doses of oseltamivir did not affect the single-dose pharmacokinetics of acetaminophen.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term carcinogenicity tests with oseltamivir are underway but have not been completed. However, a 26-week dermal carcinogenicity study of oseltamivir carboxylate in FVB/Tg.AC transgenic mice was negative. The animals were dosed at 40, 140, 400 or 780 mg/kg/day in two divided doses. The highest dose represents the maximum feasible dose based on the solubility of the compound in the control vehicle. A positive control, tetradecanoyl phorbol-13-acetate administered at 2.5 μg per dose three times per week gave a positive response.

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

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

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.

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.

Geriatric Use

The safety of TAMIFLU 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 **INDICATIONS AND USAGE: Description of Clinical Studies: Studies in Naturally Occurring Influenza: Treatment of Influenza: Geriatric Patients**).

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 **INDICATIONS AND USAGE: Description of Clinical Studies: Studies in Naturally Occurring Influenza: Prophylaxis of Influenza: Adult Patients**).

Pediatric Use

The safety and efficacy of TAMIFLU in pediatric patients younger than 1 year of age have not been studied. TAMIFLU is not indicated for either treatment or prophylaxis of influenza in pediatric patients younger than 1 year of age because of uncertainties regarding the rate of development of the human blood-brain barrier and the unknown clinical significance of non-clinical animal toxicology data for human infants (see **ANIMAL TOXICOLOGY**).

ANIMAL TOXICOLOGY
In a 2-week study in unweaned rats, administration of a single dose of 1000 mg/kg oseltamivir phosphate to 7-day-old rats resulted in deaths associated with unusually high exposure to the prodrug. However, at 2000 mg/kg, there were no deaths or other significant effects in 14-day-old unweaned rats. Further follow-up investigations of the unexpected deaths of 7-day-old rats at 1000 mg/kg revealed that the concentrations of the prodrug in the brains were approximately 1500-fold those of the brains of adult rats administered the same oral dose of 1000 mg/kg, and those of the active metabolite were approximately 3-fold higher. Plasma levels of the prodrug were 10-fold higher in 7-day-old rats as compared with adult rats. These observations suggest that the levels of oseltamivir in the brains of rats decrease with increasing age and most likely reflect the maturation stage of the blood-brain barrier. No adverse effects occurred at 500 mg/kg/day administered to 7- to 21-day-old rats. At this dosage, the exposure to prodrug was approximately 800-fold the exposure expected in a 1-year-old child.

ADVERSE REACTIONS

Treatment Studies in Adult Patients

A total of 1171 patients who participated in adult phase III 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 degree and usually occurred on the first 2 days of administration. Less than 1% of subjects discontinued prematurely from clinical trials due to nausea and vomiting.

Adverse events that occurred with an incidence of ≥1% in 1440 patients taking placebo or TAMIFLU 75 mg twice daily in adult phase III treatment studies are shown in **Table 3**. This summary includes 945 healthy young adults and 495 "at risk" patients (elderly patients and patients with chronic cardiac or respiratory disease). Those events reported numerically more frequently in patients taking TAMIFLU compared with placebo were nausea, vomiting, bronchitis, insomnia, and vertigo.

Prophylaxis Studies in Adult Patients

A total of 4187 subjects (adolescents, healthy adults and elderly) participated in phase III 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 3**). 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 3 Most Frequent Adverse Events in Studies in Naturally Acquired Influenza in Patients 13 Years of Age and Older

	Treatment				**Prophylaxis**			
Adverse Event	**Placebo N=716**		**Oseltamivir 75 mg bid N=724**		**Placebo /No Prophylaxis[a] N=1688**		**Oseltamivir 75 mg qd 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] The majority of subjects received placebo; 254 subjects from a randomized, open-label post exposure prophylaxis study in households did not receive placebo or prophylaxis therapy.

Adverse events included are: all events reported in the treatment studies with frequency ≥1% in the oseltamivir 75 mg bid group.

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 Patients

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

Adverse events occurring in ≥1% of pediatric patients receiving TAMIFLU treatment are listed in **Table 4**. The most frequently reported adverse event was vomiting. Other events reported more frequently by pediatric patients treated with TAMIFLU included abdominal pain, epistaxis, ear disorder, and conjunctivitis. These events generally occurred once and resolved despite continued dosing. They did not cause discontinuation of drug in the vast majority of cases.

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

Prophylaxis in Pediatric Patients

Pediatric patients aged 1 to 12 years participated in a postexposure prophylaxis study in households, both as index cases (134) and as contacts (222). Gastrointestinal events were the most frequent, particularly vomiting. The adverse events noted were consistent with those previously observed in pediatric treatment studies (see **Table 4**).

Table 4 Most Frequent Adverse Events Occurring in Children Aged 1 to 12 Years in Studies in Naturally Acquired Influenza

	Treatment Trials[a]				Household Prophylaxis Trial[b]			
Adverse Event	**Placebo N=517**		**Oseltamivir 2 mg/kg bid N=515**		**No Prophylaxis[c] N=87**		**Prophylaxis with Oseltamivir QD[c] 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] Pooled data from Phase III trials of TAMIFLU treatment of naturally acquired influenza.
[b] 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.
[c] Unit dose = age-based dosing

Age		Prophylaxis (10days)
1-2 years		30 mg QD
3-5 years		45 mg QD
6-12 years		60 mg QD

Adverse events included in Table 4 are: all events reported in the treatment studies with frequency ≥1% in the oseltamivir 75 mg bid group.

Observed During Clinical Practice

The following adverse reactions have been identified during postmarketing 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: Dermatitis, rash, eczema, urticaria, erythema multiforme, Stevens-Johnson-Syndrome, toxic epidermal necrolysis (see PRECAUTIONS).

Digestive: Hepatitis, liver function tests abnormal

Cardiac: Arrhythmia

Neurologic: Seizure, confusion

Metabolic: Aggravation of diabetes

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.

DOSAGE AND ADMINISTRATION
TAMIFLU may be taken with or without food (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**). However, when taken with food, tolerability may be enhanced in some patients.

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 oral suspension for pediatric patients 1 year and older or adult patients who cannot swallow a capsule is:

Body Weight in kg	**Body Weight in lbs**	**Recommended Dose for 5 Days**	**Number of Bottles Needed to Obtain the Recommended Dose**
≤15 kg	≤33 lbs	30 mg twice daily	1
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg twice daily	2
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg twice daily	2
>40 kg	>88 lbs	75 mg twice daily	3

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, 5.0 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

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. 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 oral suspension for pediatric patients 1 year and older following close contact with an infected individual is:

Body Weight in kg	**Body Weight in lbs**	**Recommended Dose for 10 Days**	**Number of Bottles Needed to Obtain the Recommended Dose**
≤15 kg	≤33 lbs	30 mg once daily	1
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg once daily	2
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg once daily	2
>40 kg	>88 lbs	75 mg once daily	3

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, 5.0 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. Prophylaxis in patients 1 to 12 years of age has not been evaluated for longer than 10 days duration. Therapy should begin within 2 days of exposure.

Special Dosage Instructions

Hepatic Impairment

The safety and pharmacokinetics in patients with hepatic impairment have not been evaluated.

Renal Impairment

For plasma concentrations of oseltamivir carboxylate predicted to occur following various dosing schedules in patients with renal impairment (see **CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations)**.

Treatment of Influenza

Dose adjustment is recommended for 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 undergoing routine hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

Prophylaxis of Influenza

For the prophylaxis of influenza, dose adjustment is recommended for 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 oral suspension every day. No recommended dosing regimens are available for patients undergoing routine hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

Geriatric Patients

No dose adjustment is required for geriatric patients (see **CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations** and **PRECAUTIONS**).

Preparation of TAMIFLU Oral Suspension

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

1. Tap the closed bottle several times to loosen the powder.
2. Measure **23 mL** of water in a graduated cylinder.
3. Add the total amount of water for constitution to the bottle and shake the closed bottle well for 15 seconds.
4. Remove the child-resistant cap and push bottle adapter into the neck of the bottle.
5. 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.

NOTE: SHAKE THE TAMIFLU ORAL SUSPENSION WELL BEFORE EACH USE.

The constituted oral suspension should be used within 10 days of preparation; 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.

HOW SUPPLIED

TAMIFLU Capsules

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

Storage

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

TAMIFLU for Oral Suspension

Supplied as a white powder blend for constitution to a white tutti-frutti–flavored suspension. Available in glass bottles containing 25 mL of suspension after constitution equivalent to 300 mg oseltamivir base. Each bottle is supplied with a bottle adapter and 1 oral dispenser (NDC 0004-0810-95).

Storage

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

Store constituted suspension under refrigeration at 2º to 8ºC (36º to 46ºF). Do not freeze.

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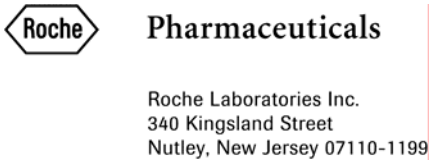


Licensor:

Gilead Sciences, Inc.
Foster City, California 94404

XXXXXXXX

Revised: Month/Year

Patient Information

TAMIFLU®

(oseltamivir phosphate)

R_X ONLY

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

What is TAMIFLU?

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

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

What is "Flu"?

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

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

Should I get a flu shot?

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

Who should not take TAMIFLU?

Do not take TAMIFLU if you are allergic to the main ingredient, oseltamivir phosphate, or to any other ingredients of TAMIFLU. Before starting treatment, make sure your health care professional knows if you take any other medicines, or are pregnant, planning to become pregnant, or breastfeeding. TAMIFLU is normally not recommended for use during pregnancy or nursing, as the effects on the

unborn child or nursing infant are unknown. TAMIFLU is not recommended for use in children younger than 1 year of age.

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

How should I take TAMIFLU?

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

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

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

TAMIFLU has not been studied in children 1 to 12 years of age for preventing flu during an outbreak in your community or for use for more than 10 days.

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

If you are taking TAMIFLU liquid, your pharmacist will give you a dosing dispenser marked with three possible doses. Follow your health care professional's instructions on which dose to take or how to combine them for the proper dose for you. In order to be sure you receive the proper dose, it is important that you use the dispenser provided. Review the instructions below on how to use the dispenser and ask your pharmacist if you have any questions. If you lose or damage the dispenser and cannot use it, contact your health care professional or pharmacist for advice on the proper dose.

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

What are the possible side effects of TAMIFLU?

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

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

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

How and where should I store TAMIFLU?

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

TAMIFLU suspension should be stored under refrigeration at 36º to 46ºF (2º to 8ºC). Do not freeze.

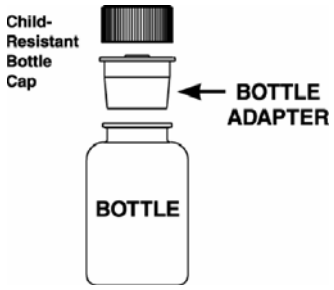
General advice about prescription medicines:

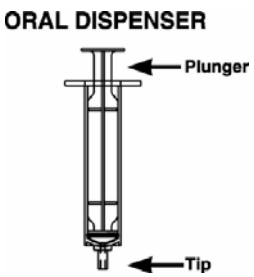
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TAMIFLU for a condition for which it was not prescribed. Do not give TAMIFLU to other people, even if they have the same symptoms you have. It may not be right for them.

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

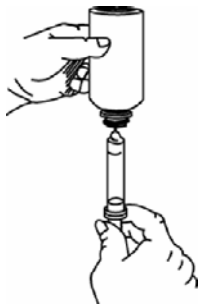
DOSING INSTRUCTIONS FOR PATIENTS:

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





- Shake closed bottle well for about 5 seconds before each use.
- Remove child-resistant cap.
- Before inserting the tip of the oral dispenser into bottle adapter, push the plunger completely down toward the tip of the oral dispenser. Insert tip firmly into opening of the bottle adapter.
- Turn the entire unit (bottle and oral dispenser) upside down.
- Pull the plunger out slowly until the desired amount of medication is withdrawn into the oral dispenser (see figure). The 75 mg dose is obtained by filling the dispenser twice, once to the 30 mg graduation, and a second fill to the 45 mg graduation.

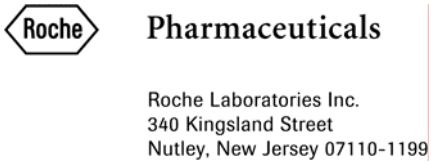


- Turn the entire unit right side up and remove the oral dispenser slowly from the bottle.
- Dispense directly into mouth. Do not mix with any liquid prior to dispensing.
- Close bottle with child-resistant cap after each use.
- Disassemble oral dispenser, rinse under running tap water and air dry prior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

Manufactured by:

F. Hoffmann-La Roche Ltd.
Basel, Switzerland

Distributed by:



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Foster City, California 94404

Revised: Month Year

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21246/S-017

MEDICAL REVIEW(S)

M E M O R A N D U M

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

DATE: 12/15/05

FROM: Katherine A. Laessig, M.D.
Division of Antiviral Drug Products, HFD-530

TO: Division File

SUBJECT: Group Leader Memo for NDA 21-246 SE5-017 and NDA 21-087 SE5-030 Efficacy Supplements for TAMIFLU (oseltamivir phosphate capsules and oral suspension)

1.0 Background

Tamiflu is the tradename for oseltamivir phosphate, which is a neuraminidase inhibitor of influenza virus. Tamiflu capsules were approved in October 1999 for the treatment of uncomplicated influenza infection in adults. In December 2000, Tamiflu oral suspension was approved along with a new indication of prevention of influenza in adults and adolescents 13 years of age and older. This efficacy supplement is submitted to extend the indication for prophylaxis to pediatric patients > 1 year of age. The basis for extending the prophylaxis indication is a household transmission study WV 16193 that included 134 pediatric index cases who received Tamiflu as treatment, and an additional 222 children who were household contacts. For complete details, please refer to the medical officer review by Dr. Linda Lewis, and the biometrics review by Dr. Tom Hammerstrom.

2.0 Summary of Study Results

Study WV 16193 was a randomized, open-label study to evaluate the effect of Tamiflu given once daily for 10 days as prophylaxis to household contacts of index cases with clinical influenza who were receiving treatment with Tamiflu appropriately dosed for their ages (not weight-based). Household contacts were included if they were $\geq$ 1 year of age. Analysis of the subgroup of study participants aged 1-12 years provides the basis for extending the approved population for prophylaxis.

The primary efficacy endpoint was the proportion of households with at least one secondary case of febrile, laboratory confirmed influenza (fever $\geq$ 37.8 plus cough and/or coryza) during the 10 day period following the start of treatment of the index case. Laboratory confirmation was based on detection of viral shedding within 2 days of the time that fever was reported, and/or a fourfold or

greater rise in influenza-specific antibody levels between the baseline and day 30 sample.

Two hundred seventy-seven households of 296 index cases (all index cases received bid treatment with Tamiflu) were enrolled and randomized 1:1 to either once daily prophylaxis with Tamiflu for 10 days or treatment with Tamiflu if they developed influenza-like illness for 5 days. Of these, 139 households with 392 contact subjects were randomized to the no prophylaxis arm while 138 households with 416 contacts were randomized to prophylaxis with Tamiflu. Eight index cases withdrew from the study, compared to 13 withdrawals in the treatment arm and 8 withdrawals in the prophylaxis arm.

Based on the intent-to-treat (ITT) analysis, 20% of subjects in the treatment group developed febrile laboratory-confirmed influenza compared to 7% of subjects in the prophylaxis group. Sensitivity analyses of the treatment effect included evaluation of the ITT subpopulation that included index cases who had laboratory-confirmed influenza at baseline (ITTII) and the ITT subpopulation of index cases with laboratory-confirmed influenza at baseline and contact cases not infected at baseline (ITTIINAB). These sensitivity analyses confirmed the prophylactic treatment effect of Tamiflu such that 26% of contacts in treatment group of the ITTII population developed laboratory-confirmed influenza infection compared to 11% of the prophylaxis group. For the ITTIINAB analysis, 22% of subjects in the treatment group developed laboratory confirmed influenza, compared to 5% of the prophylaxis group. Thus, the protective efficacy of Tamiflu prophylaxis (1.0-relative risk) ranged from 63% to 79%, depending upon which population was analyzed.

For the pediatric subpopulation of WV16193, similar results were demonstrated by a protective efficacy of 64% for the ITT population, 55% for the ITTII population, and 80% for the ITTIINAB population. The treatment effect that will be described in the product labeling is the reduction in influenza infection reported in contacts not infected at baseline (ITTIINAB). Among subjects who received prophylaxis, only 3% developed laboratory-confirmed influenza compared to 17% of those not receiving prophylaxis.

3.0 Summary of Safety

The safety analyses included all subjects who received at least one dose of study drug, either for treatment or prophylaxis, and subjects who received no Tamiflu. There were no deaths reported during the study. There were 5 SAEs reported during the study, 3 in subjects receiving Tamiflu and 2 in subjects who did not receive Tamiflu. None were considered as related to study drug.

Twenty-eight subjects withdrew from the study prematurely, of which 5 were due to AEs considered to be possibly or probably study drug related. These events included 4 nausea and vomiting and 1 allergic/hypersensitivity reaction.

The adverse events occurring during the study were not markedly different from those previously identified during clinical studies of Tamiflu. The most common AEs are nausea and vomiting, occurring in up to 10% if subjects. Notably, the rates of GI AEs appeared to be somewhat higher in the pediatric subpopulation of whom up to 30% experienced vomiting. A dose response relationship is suggested by the data as well, such that higher rates of GI adverse events occur in subjects receiving the higher treatment dose of Tamiflu than in those receiving the prophylaxis dose. There was no laboratory data obtained in this trial, since an adequate of the effect of Tamiflu on various laboratory parameters was obtained in the original treatment trials of Tamiflu.

During the review cycle, a consult was obtained from the Office of Drug Safety to review the post-marketing reports of the AERS database associated with Tamiflu use. Cases of serious hepatic, renal, neuropsychiatric, and skin/hypersensitivity reactions were assessed. Of these, only the serious skin/hypersensitivity reactions appeared to be a new safety signal that was not addressed adequately in the product labeling and changes to the PRECAUTION section of the label have been agreed to by the applicant, Hoffmann La Roche, Inc.

4.0 Recommendation

This efficacy supplement containing the results of study WV16193 demonstrates substantive evidence of the safety and efficacy of Tamiflu prophylaxis of influenza A and B for the pediatric population aged 1 to 12 years. Therefore, I concur with the findings of the medical officer review by Dr. Linda Lewis, and recommend that this application be approved.

Katherine A. Laessig, M.D.

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

/s/

Kathrine Laessig
12/20/2005 04:28:57 PM
MEDICAL OFFICER

Debra Birnkrant
12/21/2005 09:01:30 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDAs 21-246 and 21-087
Submission Number	017
Submission Code	SE5
Letter Date	April 15, 2005
Stamp Date	April 18, 2005
PDUFA Goal Date	February 18, 2006
Reviewer Name	Linda L. Lewis, M.D.
Review Completion Date	December 19, 2005
Established Name	Oseltamivir phosphate
Trade Name	Tamiflu®
Therapeutic Class	Antiviral
Applicant	Hoffman-La Roche, Inc.
Priority Designation	Standard
Formulation	Capsules and oral suspension
Dosing Regimen	75 mg QD for adults Weight-based dosing QD for pediatric patients
Indication	Prophylaxis of influenza A or B infection in households
Intended Population	Patients $\geq$ 1 year of age

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This efficacy supplement to NDA 21-246 and NDA 21-087 was submitted to support the extension of the influenza prophylaxis indication for Tamiflu to patients 1 to 12 years of age. It is the opinion of the Medical Officer completing this Clinical Review that Tamiflu should be approved for use in prophylaxis of influenza in this age group and recommended for a period of 10 days following close contact with an infected individual. This recommendation is based on review of the efficacy and safety data from Study WV16193 submitted by Hoffmann-La Roche, Inc. The regimen of once daily Tamiflu (75 mg in patients ≥ 13 years of age and weight-based in those 1 to 12 years of age) was shown to be effective in reducing household transmission of influenza in households where the index cases were also treated with Tamiflu. This regimen was found to be safe in the population studied. No deficiencies were identified in the submission that would preclude approval of this regimen.

No data were provided to support approval of prophylaxis dosing in patients 1 to 12 years of age for periods longer than 10 days (b) (4) Additional data supporting the safety of a longer prophylaxis regimen has been requested as a Phase 4 commitment.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Tamiflu has been approved for the treatment of influenza in patients > 1 year of age and for prophylaxis in patients ≥ 13 years of age. To date, no special risk management strategies have been proposed by the applicant or requested by the FDA. The applicant continues to provide safety updates in the form of Annual Reports. The applicant also collects post-marketing reports of adverse events through their global safety network which are then submitted to the FDA Adverse Event Reporting System (AERS) database. During active influenza season when drug use is highest, AERS cases related to all influenza antiviral drugs are monitored in an on-going basis by the Safety Reviewer (Office of Drug Safety, Division of Drug Risk Evaluation) and the Clinical Reviewer (Division of Antiviral Products, Center for Drug Evaluation and Research).

1.2.2 Required Phase 4 Commitments

(b) (4)

The DAVP Review Team has requested the following post-marketing commitment:

> Collect and submit safety data in a population of 40-50 pediatric patients 1 to 12 years of age using the approved prophylaxis dosing recommendations for a period of up to 6 weeks in the setting of seasonal influenza prophylaxis. Evaluation of "influenza high risk" patient groups is suggested.
> Submit protocol by December 1, 2006
> Begin study by 2006-07 influenza season
> Submit final study report by July 1, 2008

1.2.3 Other Phase 4 Requests

No additional recommended or optional post-marketing commitments related to this supplement are suggested.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Tamiflu (oseltamivir phosphate) is an ethyl ester pro-drug of the selective influenza virus neuraminidase inhibitor Ro 64-0802 (oseltamivir carboxylate). The drug has previously been shown to have good oral bioavailability in capsule and suspension formulations and a half-life that allows twice daily dosing for treatment.

Tamiflu was approved for the treatment of influenza in patients $\geq$ 13 years of age in November, 1999, at a dose of 75 mg given twice daily for 5 days. It was approved for treatment in patients 1 to 12 years of age in December, 2000, with pediatric dosing recommended as a fixed dose based on weight categories given twice daily for 5 days. Approval for use in treatment was based on review of randomized, placebo-controlled studies of naturally occurring influenza in both adult and pediatric patients, including some subgroups considered at higher risk for complication of influenza (eg., the elderly, patients with asthma).

Tamiflu was also approved for use as prophylaxis against influenza in patients $\geq$ 13 years of age in December, 2000, at a dose of 75 mg given once daily. Approval for this indication was based on review of randomized, controlled studies of both household or institutional transmission (post-exposure prophylaxis for 7 days) and transmission during a community outbreak (seasonal

prophylaxis for up to 6 weeks). Prophylaxis was previously shown to be effective when given within 48 hours of exposure and the prophylaxis effect lasted for as long as Tamiflu was given.

The current submission provides the final study report and electronic datasets containing safety and efficacy data from Study WV16193. This was a randomized, open-label study to evaluate the benefit of Tamiflu given once daily for 10 days to household contacts of index cases with clinical influenza. All index cases were treated with the approved dose of Tamiflu for their ages. Unlike the earlier prophylaxis studies, in Study WV16193 index cases and contacts included children 1 to 12 years of age as well as older subjects. At the request of the Review Team, the applicant provided a cumulative summary of all serious hepatic, renal, dermatologic, and neurologic adverse events reported to their safety database since the original approval.

A total of 1110 patients from 1 to 83 years of age enrolled in Study WV16193, 298 as index cases and 812 as contacts. In this study, 277 households were randomized to receive either prophylaxis for 10 days (138 households, 560 patients) or no prophylaxis but treatment if ill (139 households, 550 patients). The study provides an adequate database for assessment of the safety and efficacy in a previously unstudied age group, patients 1 to 12 years of age. In this age group there were 134 index cases and 222 contacts (107 randomized to Prophylaxis and 115 randomized to No Prophylaxis).

1.3.2 Efficacy

FDA review of the clinical, virologic, and serologic endpoint data collected in Study WV16193 supports the approval of Tamiflu as prophylaxis for influenza in patients 1 to 12 years of age. The primary efficacy endpoint for this study was the proportion of households in which at least one contact developed laboratory-confirmed, clinical influenza within 10 days of the beginning of treatment for the index case. This endpoint was agreed upon at the time of the protocol review and was considered to be an appropriate measure of the burden of influenza in a household. Secondary endpoints included the proportion of contacts who developed laboratory-confirmed, clinical influenza, the proportions of households or contacts who developed any laboratory-confirmed influenza (including mildly symptomatic or asymptomatic illness), and the duration of fever and clinical symptoms among contacts who developed confirmed influenza.

The study was designed to allow evaluation of the contribution of Tamiflu prophylaxis in reducing transmission of influenza in households beyond the effect of treating the index case. The only significant limitation of the study was that households were randomized to Prophylaxis or No Prophylaxis (symptomatic treatment) but neither contacts nor investigators were blinded to the assigned treatment group. While this is unlikely to have any impact on virus cultures or influenza serology, it may have had some impact on the assessment of more subjective influenza symptoms and adverse events. However, the lack of blinding was not considered to have a major impact on the results of the study.

Based on the results of Study WV16193, the DAVP Review Team concluded that Tamiflu administered once daily as prophylaxis was effective in limiting household transmission among exposed contacts when they were provided prophylaxis for 10 days beginning within 48 hours of

identification and start of treatment of the index case. The benefit of prophylaxis was shown in both adults and adolescents ≥ 13 years of age, the group for whom Tamiflu is currently indicated for prophylaxis, and in household contacts 1 to 12 years of age. Independent FDA statistical analysis of the study data confirmed that the risk of at least one new contact (not shedding influenza virus at baseline) per household developing laboratory-confirmed, clinical influenza in the setting of confirmed infection in the index case was reduced from 22% in households not receiving prophylaxis to 5% in those receiving Tamiflu once daily (P=0.0004). Similarly, the risk of confirmed, clinical influenza among individual contacts not already shedding influenza virus at baseline was reduced from 11% in those contacts not receiving prophylaxis to 2% in those receiving Tamiflu (P<0.0001). If all confirmed influenza infections (symptomatic and asymptomatic) were evaluated, the proportion of contacts developing influenza was significantly reduced in those contacts receiving prophylaxis and the proportion of households with at least one new case of influenza trended the same direction but did not reach significance. The FDA statistical analysis also confirmed that the duration of influenza illness appeared to be shorter in those contacts who developed influenza while receiving prophylaxis compared to those who did not receive prophylaxis.

The benefit of prophylaxis was also confirmed in the age subgroup targeted in this submission, pediatric patients 1 to 12 years of age. In this subgroup, the proportion of contacts not shedding influenza virus at baseline who developed confirmed, clinical influenza decreased from 17% in those not receiving prophylaxis to 3% in those receiving prophylaxis (P=0.0006). Although the study was not initially designed to show the benefit of prophylaxis specifically in pediatric patients, this study provides adequate data for assessing the efficacy of household prophylaxis in patients 1-12 years of age.

The approval of Tamiflu for prophylaxis of influenza in patients 1 to 12 years of age provides the first approved regimen for prophylaxis of both influenza A and B in pediatric patients and the first pediatric prophylaxis indication for a neuraminidase inhibitor.

1.3.3 Safety

The safety profile of Tamiflu has been evaluated in treatment studies conducted in all age groups ≥ 1 year of age and in prophylaxis studies conducted in subjects ≥ 13 years of age. Study WV16193 provides comparative data for both adult and pediatric patients receiving 2 different regimens of Tamiflu (treatment or prophylaxis) or no treatment. In this study 1104 study participants received at least one dose of study drug and were included in the safety analysis. The results for this study were consistent with earlier studies that were randomized and blinded and it is unlikely that the lack of blinding in this study significantly affected the safety conclusions.

No new safety findings emerged during the review of Study WV16193. The most commonly reported adverse events that appear to be related to Tamiflu include gastrointestinal events such as vomiting. Vomiting also appears to be dose-related. In the full study population, vomiting occurred in about 10% of study subjects receiving Tamiflu twice daily (treatment), 5% of subjects receiving Tamiflu once daily (prophylaxis), and <1% of those receiving no Tamiflu.

Among the subgroup of children 1 to 12 years of age, vomiting occurred in 20% of those receiving Tamiflu twice daily, 10% of subjects receiving Tamiflu once daily, and 2% of those receiving no Tamiflu. No deaths were reported during the study period. Five study subjects developed serious adverse events requiring hospitalization but none of these events were considered related to study drug. Similarly, 5 study subjects discontinued their Tamiflu treatment or prophylaxis prematurely because of adverse events. Three of the 5 subjects who prematurely discontinued study drug did so because of nausea and/or vomiting. These findings are very similar to those documented in previously reviewed studies evaluating Tamiflu for treatment or prophylaxis.

As part of this efficacy supplement, the Office of Drug Safety, Division of Drug Risk Evaluation, was asked to conduct a post-marketing review of the FDA's Adverse Event Reporting System (AERS) focusing on serious hepatic, renal, skin/hypersensitivity, and neuropsychiatric events. A search of the AERS database identified 21 cases of serious hepatic toxicity, including 14 cases of hepatic failure, and 43 cases of serious renal toxicity, including 18 cases of renal failure. These cases were confounded by the use of other medications and the presence of other medical conditions. None of these cases appeared to have a clear causal relationship with Tamiflu. The AERS search identified 126 reports of neuropsychiatric adverse events, including 3 deaths. Most of these cases were reported in pediatric patients. The etiology of these events and a possible relationship to Tamiflu use was frequently difficult to interpret because many of the reports lacked sufficient detail to assess causality and many of the reports were from foreign sources (especially Japan). Some events such as delirium, convulsions, and altered consciousness were also similar to events that have been described in association with influenza. Other events described as "abnormal behavior" were unusual and not completely explained as a manifestation of influenza. Although no change in labeling regarding neuropsychiatric events is currently recommended, DDRE and the DAVP Review Team will continue to monitor closely for this type of events as Tamiflu use increases in the U.S. population. A total of 43 cases of serious skin/hypersensitivity reactions were identified in the AERS search. As with the neuropsychiatric cases, a majority of the reports were from Japan but there were also reports from the U.S., Europe, and Australia. Unlike the other categories of events, a majority of the serious skin reactions were considered likely to be associated with Tamiflu use. These findings prompted DDRE and the DAVP Review Team to recommend new safety language regarding serious skin/hypersensitivity reactions in the Tamiflu label.

1.3.4 Dosing Regimen and Administration

The doses used for prophylaxis and treatment in patients 1 to 12 years of age in Study WV16193 were based on age. (b) (4)

The approved dose for prophylaxis of influenza in patients ≥ 13 years of age is Tamiflu 75 mg given once daily, half the approved treatment dose. In all previous prophylaxis studies, this dosing regimen was shown to be effective. The selection of dosing for pediatric patients is also

half the treatment dose. The DAVP Review Team continues to believe that weight-based dosing is appropriate for the U.S. pediatric population and does not feel that an extrapolation of the study results to a weight-based dose recommendation is problematic. The prophylaxis doses recommended for patients 1 to 12 years of age are:

≤ 15 kg (≤ 33 lb)	30 mg QD x 10 days
> 15 kg – 23 kg (> 33 lb – 51 lb)	45 mg QD x 10 days
> 23 kg – 40 kg (> 51 lb – 88 lb)	60 mg QD x 10 days
> 40 kg (> 88 lb)	75 mg QD x 10 days

Previously, Tamiflu was recommended for a period of 7 days following close contact with an infected person (post-exposure prophylaxis). The current study evaluated a post-exposure prophylaxis of 10 days. Efficacy of the 7-day regimen has not been evaluated in pediatric patients but both regimens have acceptable safety profiles. To provide consistent recommendations for post-exposure prophylaxis, the recommendations for dosing adults and adolescents will be revised to reflect the 10-day regimen.

(b) (4)

the DAVP Review Team has requested that the applicant collect safety data in pediatric patients given up to 6 weeks of Tamiflu in the setting of community outbreak (seasonal prophylaxis).

1.3.5 Drug-Drug Interactions

Absorption, distribution, metabolism, and excretion of Tamiflu have been previously evaluated and these investigations show that the drug is not significantly metabolized but is predominantly excreted unchanged by the kidneys. There is potential for drug exposure to be altered by other conditions or drugs that impair renal function. It is also possible that Tamiflu could compete with other drugs excreted by the kidneys but no specific drug-drug interactions have been identified. No drug-drug interaction studies were submitted with this supplement and none have been requested as a result of this review.

1.3.6 Special Populations

This study addresses the safety and efficacy of once daily dosing of Tamiflu for prophylaxis of influenza in household contacts of index cases with clinical influenza and provides data for a previously unstudied population, pediatric patients 1 to 12 years of age. In earlier studies, other special populations have been addressed including elderly patients, those with impaired renal function, and patients at higher risk for complications of influenza. As a Phase 4 commitment following an earlier efficacy supplement, the applicant was asked to investigate the safety and effectiveness of Tamiflu for the treatment and prophylaxis of influenza in immunocompromised patients.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

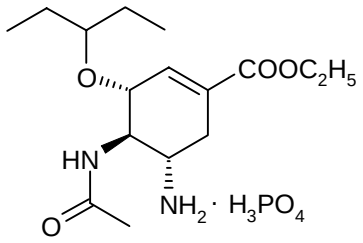
Description: Tamiflu® (oseltamivir phosphate) is an ethyl ester pro-drug of the selective influenza virus neuraminidase inhibitor Ro 64-0802 (oseltamivir carboxylate).

Established name and trade name: Oseltamivir phosphate (Tamiflu®)

Pharmacological class: Antiviral

Indications, dosing regimens, age groups: Tamiflu is approved for the treatment of influenza A or B in patients $\geq$ 1 year of age and for prophylaxis of influenza in patients $\geq$ 13 years of age. Dosing in adults is 75 mg BID for 5 days for treatment or 75 mg QD for prophylaxis. Prophylaxis dosing is for 7 days for post-exposure prophylaxis or for up to 6 weeks for seasonal prophylaxis. Dosing for treatment in pediatric patients is based on weight bands and is given BID for 5 days. The proposed indication in this supplement is for Tamiflu for prophylaxis of influenza A and B in patients > 1 year of age using weight-based dosing on a QD schedule.

Chemical structure:



2.2 Currently Available Treatment for Indications

Currently available antiviral agents for the treatment of influenza include amantidine (Symmetrel) and rimantidine (Flumadine), inhibitors of the influenza A M2 ion channel, and zanamivir (Relenza), another neuraminidase inhibitor. Amantidine and rimantidine which are approved for prophylaxis in pediatric patients > 1 year of age, are active only against influenza A. They have no activity against influenza B, which lacks the M2 protein, and have significant adverse effect profiles. Zanamivir, which is delivered via a disk inhaler device, is approved for treatment of influenza in children 7 years or older but not in younger children and is not approved for prophylaxis.

2.3 Availability of Proposed Active Ingredient in the United States

Tamiflu is available in the U.S. as 75 mg capsules and as a powder for constitution to an oral suspension (12 mg/mL). The capsule formulation of Tamiflu was approved for the treatment of uncomplicated influenza infection in adults in October, 1999 (NDA 21-087). A supplement to that NDA for the prevention of influenza in adults and adolescents (13 years and older) was approved in November, 2000. The original approval of NDA 21-246 for Tamiflu oral suspension extended the indication for Tamiflu to treat acute influenza in children older than 1 year of age. The current efficacy supplement seeks to extend the indication for prophylaxis to pediatric patients > 1 year of age. The capsule and suspension formulations are described in a single product label.

(b) (4)

Major steps in this manufacturing process are conducted at the primary Hoffman-La Roche site in Basel, Switzerland. Because of increasing concern that an influenza pandemic could disrupt global supply systems, the applicant and the FDA have recently completed approval of additional manufacturing sites in the U.S., ensuring an all-domestic production process. (b) (4)

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This submission contains the final clinical study report for Roche's Study WV16193, a multinational, randomized study of household prophylaxis of influenza. (b) (4)

The current submission provides both raw data and analysis datasets for Study WV16193 and proposed labeling to extend the age range of the prophylaxis indication. Source material included electronic datasets containing demographic, safety, and efficacy data from the study and an PDF copy of the study report. Datasets were submitted to the CDER Electronic Document Room as SAS transport files in accordance with FDA recommendations regarding electronic submissions. Since the supplement contains data from only a single study, this study is described in detail in the body of this review and not as an Appendix.

In addition, the applicant was asked to provide a safety update on all reported cases of serious renal, hepatic, skin/soft tissue, and central nervous system toxicity from their cumulative safety database. This update, dated June 10, 2005, was provided as an electronic amendment to the NDA supplement and is described in more detail in Section 7.2.9.

4.3 Review Strategy

The Clinical Review of this efficacy supplement was conducted by Dr. Linda Lewis (Medical Officer) who assessed the overall study design and safety profile of Tamiflu in Study WV16193 and the applicant's efficacy analysis. The Medical Officer analyzed rates of clinical adverse events using the JMP Statistical Discovery software. The Clinical Review was complemented by a Statistical Review of efficacy endpoint analyses, sensitivity analyses, and subgroup analyses for the clinical trial conducted by Dr. Tom Hammerstrom, Mathematical Statistics Reviewer. The safety update information was also forwarded to the Office of Drug Safety (ODS) and a consult was requested to assist in the review of post-marketing safety data. The ODS consult was performed by Evelyne Edwards, Post-marketing Safety Evaluator, Division of Drug Risk Evaluation (DDRE).

For this review, the Clinical Review Template was used in accordance with the CDER Manual of Policies and Procedure for efficacy supplements. Since the supplement involved an approved product, some sections of the template that are not applicable to the efficacy supplement were deleted.

4.4 Data Quality and Integrity

No DSI audits were requested for this efficacy supplement.

4.5 Compliance with Good Clinical Practices

This study appears to have been conducted in compliance with GCP standards although minor protocol deviations were identified. Informed consent procedures were in use and acceptable ethical standards were followed. The study protocol and procedures and informed consent forms for each study site were reviewed and approved by that site's Institutional Review Board.

4.6 Financial Disclosures

The applicant reports that none of the investigators or sub-investigators participating in the study had interests subject to financial disclosure. Financial information was not available for 10 investigators enrolling patients in Estonia and Finland. The applicant notes that they were unable to contact these investigators to obtain the necessary financial disclosure forms.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Study WV16193 is presented as evidence of the efficacy of Tamiflu as prophylaxis against household transmission of influenza A and B in households where the index case is also treated with Tamiflu. In this study, household contacts were included if they were $\geq$ 1 year of age and the applicant is requesting extension of the age range for prophylaxis to include pediatric patients

1 through 12 years of age. Tamiflu is currently approved for treatment of influenza in patients ≥ 1 year of age with uncomplicated infection and for prophylaxis of influenza in patients ≥ 13 years of age.

6.1.1 Methods

Study WV16193 was reviewed as a single study for the primary efficacy endpoint and multiple secondary efficacy endpoints. No pooling of data with previous studies was done. The applicant's efficacy conclusions were confirmed by independent FDA analysis of the data as described in the Statistical Review conducted by Dr. Hammerstrom. In this Clinical Review, tables abstracted from the applicant's submission are referenced and the source identified. Tables generated by the Clinical Reviewer have no source citation.

6.1.2 General Discussion of Endpoints

In this study the endpoint of primary interest was the prevention of household transmission of influenza in households where the infected index case was treated with Tamiflu. Households were randomized as units so the effect on either the unit or the individual contact could be evaluated. The applicant chose as the primary efficacy endpoint the proportion of households with cases of febrile, laboratory-confirmed influenza within the household. A secondary case of clinical (febrile) confirmed influenza was defined as a contact who developed fever ≥ 37.8^{o}C plus cough and/or coryza during the 10 days following the start of treatment of the index case in the household. Confirmation of influenza as the cause of the clinical illness required either detection of viral shedding within 2 days before or after the fever was reported or a ≥ 4-fold increase in influenza-specific antibody levels between baseline and study Day 30.

In earlier household transmission studies of influenza prophylaxis a study design that did not treat the index case was used. This type of study design did not allow for separating the effect that influenza treatment might have on preventing transmission within the household. The design of Study WV16193, providing treatment of all index cases with randomization of household units to either prophylaxis or no prophylaxis allows a conclusion to be made regarding the added contribution of the prophylaxis regimen in preventing transmission within a household.

Clinical symptoms were recorded by each study participant twice daily from the initiation of treatment in the index case (Day 1) through Day 30. Each diary card requested the subject's temperature and a checklist of influenza symptoms including: nasal congestion, sore throat, cough, aches and pains, fatigue, headache, and chills/sweats. Each symptom could be marked as absent, mild, moderate, or severe in intensity. Adult and adolescent subjects were also asked to assess their general state of health ("worst possible health" to "normal health for someone your age"), their sleep pattern ("worst quality sleep" to "normal pre-flu sleep"), and their ability to perform their usual activities ("unable to perform" to "normal ability to perform"). For children < 13 years of age, the diary card asked the adult caregiver to rate the symptoms of cough and nasal congestion as no problem, minor problem, moderate problem, or major problem and asked

for an assessment of the child's general state of health ("worst possible health" to "normal health"). All health assessments were circled on an analog scale from 1 to 10.

In the case of respiratory viral illnesses like influenza, early symptoms may not be specific for influenza and a clinical diagnosis followed by virologic or serologic confirmation of infection is considered acceptable evidence of influenza-associated illness. Efficacy analyses typically include evaluations of clinical disease, confirmed infection regardless of clinical status, and laboratory-confirmed clinical disease. It is also common for applicants to include some type of evaluation of patient perception of illness or quality of life, although these analyses are not considered adequate evidence of effective treatment and have not been used in labeling.

6.1.3 Study Design

Study WV16193 was an open-label, randomized study in which households of at least 3 members were enrolled as a group. Index cases who were $\geq$ 1 year of age and had symptoms of influenza for < 48 hours were identified and treated with the approved dose of Tamiflu (BID for 5 days). When an index case was identified, household contacts were randomized as a unit to receive either: active treatment at the time they developed symptoms of influenza-like illness (Group T, No Prophylaxis group) or prophylaxis with Tamiflu for 10 days following the onset of influenza-like symptoms in the index case (Group P, Prophylaxis group). All contacts within the same household were randomized to receive the same study regimen. Eligible contacts were required to have been in residence in the household with the index case for at least 2 days before the onset of symptoms of influenza-like illness and at least 3 days after initiation of the study. Children < 1 year of age were not allowed to participate in the study but were noted in the study data collection. A minimum of 400 households were planned for enrollment (200 per treatment arm).

Households were recruited prior to influenza season and informed consent could be signed up to 6 months before study entry. Inclusion criteria for index cases included: age $\geq$ 1 year, rapid onset of symptoms consistent with influenza, fever $\geq$ 37.8^{o}C plus cough and/or coryza at entry, less than 48 hours between onset of symptoms and start of study drug, and be a member of a household of between 3 and 8 individuals (with at least 2 eligible contacts and no more than 1 ineligible contact). Inclusion criteria for contacts included: age $\geq$ 1 year. All subjects were required to be able to sign informed consent (or have a parent or guardian who could sign informed consent). Subjects were not allowed to enter the study as either index cases or contacts if they: had significant renal disease with creatinine clearance < 30 mL/min, had significant hepatic dysfunction, had known cardiac failure, were transplant recipients on immunosuppressant therapy, had active cancer, were known to be HIV-infected, had taken antiviral drugs active against influenza within 2 weeks of study, were known to be allergic to Tamiflu or any excipients, had participated in another clinical trial within 4 weeks, were taking steroids or immunosuppressant therapy, females who were pregnant or breastfeeding, or contacts who were randomized > 48 hours after onset of illness in the index case.

Doses of Tamiflu administered during this study were slightly different than those approved for use in the U.S. for treatment of influenza but were the doses originally proposed by the applicant

and were under review at the time the study started. U.S. labeling recommends dosing of children < 13 years of age by weight-based categories. Dosing for this study was based on patient age. Both the capsule formulation (75 mg) and the oral powder for suspension (12 mg/mL after reconstitution) were used in the study. All participants 1 to 12 years of age received the suspension formulation. The following doses were used for study participants:

Prophylaxis doses:

- Children 1-2 years (inclusive) 30 mg QD x 10 days
- Children 3-5 years 45 mg QD x 10 days
- Children 6-12 years 60 mg QD x 10 days
- Adults and adolescents $\geq$ 13 75 mg QD x 10 days

Treatment doses:

- Children 1-2 years (inclusive) 30 mg BID x 5 days
- Children 3-5 years 45 mg BID x 5 days
- Children 6-12 years 60 mg BID x 5 days
- Adults and adolescents $\geq$ 13 75 mg BID x 5 days

Baseline evaluations of the index case and household contacts were performed following diagnosis of the index case and within 48 hours of the start of influenza illness. The initial evaluation for index cases included medical history, presence of influenza symptoms, review of any medications received in the prior 2 weeks, receipt of any antiviral drugs for influenza (Tamiflu or Relenza), serum samples for determination of baseline influenza-specific antibody titers, and throat and nasal swabs for influenza virus culture. Subjects were instructed in the use of the diary cards and the first diary card was completed. Diary cards tracked the administration of study drug, presence of fever and other influenza-associated symptoms, and health and functional status. They were to be completed twice daily. Subjects were allowed to take OTC medications as needed but were told to note them on their diary cards. Other antiviral drugs with activity against influenza were prohibited.

All index cases were followed through the study period. They were seen in follow-up on Day 6, following the last dose of treatment to evaluate occurrence of fever, other symptoms, adverse events, secondary illness, and to have throat and nasal swabs for influenza viral culture. On Day 10 they were evaluated again and asked to complete a questionnaire on the pharmacoeconomic impact of illness. Index cases were seen between Days 28 to 32 for a final study visit. At this visit, repeat blood samples were collected for determination of influenza antibody levels. Diary cards were completed twice daily until Day 30 of the study. If during the course of follow-up an index case developed new symptoms consistent with influenza after completion of their treatment course, they were eligible to receive a second course of Tamiflu BID for 5 days. Repeat virologic studies were performed prior to any second courses.

Eligible contact cases randomized to the Prophylaxis group received their first dose of study drug as soon as possible after diagnosis of the index case in their household and randomization. Contacts in the No Prophylaxis group entered into active study monitoring immediately

following randomization. The Day 1 diary card was completed prior to receiving study drug (or immediately following randomization). Information and laboratory tests similar to those done in index cases were performed at onset of the study period to evaluate baseline influenza status.

Contacts were followed by phone on Day 3 to evaluate any symptoms suggestive of influenza, difficulties with adherence to the prophylaxis regimen, and occurrence of AEs. Contacts in the No Prophylaxis group who developed fever plus cough and/or coryza or other symptoms of influenza notified the investigator or study nurse. These subjects were prescribed Tamiflu at the treatment dose within 48 hours of onset of symptoms and were seen in the clinic. During the illness evaluation visit, throat and nasal swabs were collected for viral culture and symptoms and AEs were recorded. Contacts continued to complete diary cards twice daily. They were re-evaluated and repeat cultures were performed after the completion of the 5 day treatment course. Contacts in the Prophylaxis group were instructed to take their dose of Tamiflu in the morning with breakfast for 10 days. They were to contact the investigator or study nurse if they developed any symptoms of influenza and a clinical evaluation was performed and viral cultures obtained. If the investigator diagnosed clinical influenza, Tamiflu was offered at the treatment doses. Similar procedures for follow-up and "re-treatment" were performed.

Contacts who continued on the Prophylaxis or No Prophylaxis regimen were evaluated in clinic on Day 10 for follow-up assessment of symptoms, AEs, and collection of viral cultures. Those in the Prophylaxis group were instructed to return their study drug pack on Day 10. All contacts continued to complete diary cards twice daily until Day 30. A final study visit was performed on Day 28 to 32 to evaluate fever and other symptoms, AEs, and to obtain blood samples for influenza antibody levels.

Efficacy measurements used during the study included the nasal and throat swabs for influenza virus culture obtained at baseline and then at the Day 6 (for index cases) or Day 10 (for contacts), and at the time of symptomatic illness and following treatment (for ill contacts). Blood for influenza specific antibody levels were collected at baseline and Day 30 for all index cases and contacts. Antibody levels for all subjects were performed at a central laboratory. This combination of measurements allowed the sponsor to identify subjects with laboratory-confirmed, clinical influenza as well as those who had asymptomatic or subclinical influenza. It also allowed identification of contacts who were already infected at the time of study entry for whom prophylaxis might not be expected to be effective.

6.1.4 Efficacy Findings

As noted in Section 6.1.2, the applicant's primary efficacy endpoint was the percentage of households with at least one secondary case of febrile, laboratory-confirmed influenza illness during the 10 day period following the start of treatment in the index case. Laboratory confirmation could be based on either detection of viral shedding within 2 days of onset of fever or a $\geq$ 4-fold rise in influenza-specific antibody levels from baseline to the Day 30 sample. Other major secondary efficacy endpoints included: the percentage of individual contacts with laboratory-confirmed, clinical influenza, the burden of illness in the household assessed as a measure of duration and severity of all influenza illness in the household during the 30 day study

period, the incidence of all influenza infection in households and individual contacts (asymptomatic or subclinical), the incidence of secondary complications in contacts, duration and severity of illness in the treated index cases, a comparison of the 2 methods of managing influenza (symptomatic treatment vs prophylaxis). The secondary endpoints were analyzed in a variety of ways using the clinical and virologic/serologic data, the health and functioning questionnaires, and the pharmacoeconomic questionnaires.

The applicant defined four populations of contacts that were used in their efficacy analyses. Different populations were appropriate for the variety of endpoints analyzed and to obtain a better understanding of the impact of the prophylaxis regimen under study. These populations of household contacts are defined as follows:

- ITT – The Intent-to-Treat population included all contacts who were randomized into the study and completed at least one diary card. This is the largest, most conservative analysis population.
- ITTII – The Intent-to-Treat Index Infected population included all contacts as randomized who were in households with an index case with laboratory confirmed influenza. This population eliminates those contacts who were not actually exposed to household influenza.
- ITTIINAB – The Intent-to-Treat Index Infected Negative at Baseline population included contacts as randomized in households with laboratory-confirmed influenza who had negative virologic studies at baseline. This population also eliminates those contacts who were already infected at the time of study entry and who were unlikely to benefit from prophylaxis.
- Standard Population – This "per protocol" population included all randomized contacts in households with laboratory-confirmed index cases who had no major protocol violations at entry or during follow-up. This population excluded contacts who were not exposed to influenza, who developed illness < 6 hours after the first dose of treatment in their index case, who were infected with a different strain of influenza than their index case, who failed to take their prophylaxis as recommended, or who had more than one person in the household who was ineligible. This population was analyzed according to the regimen actually received rather than as randomized.

Index cases were enrolled in Study WV16193 if they had symptomatic illness suggestive of influenza that included at least fever $\geq 37.8^{o}$C plus cough and/or coryza. Over 60% of index cases had confirmed influenza. The applicant notes that the predominant strain during the study was influenza A H1N1 and about 1/3 of infected index cases had influenza B. Table 6.1.4A summarizes the infection status of all index cases.

Table 6.1.4A: Infection Status of Index Cases

Infection status	Prophylaxis (N=150)	No Prophylaxis (N=148)
Infected – Yes*	90 (60%)	94 (64%)
Influenza A	56 (62%)	65 (69%)
Influenza B	34 (38%)	29 (31%)
Infected – No	60 (40%)	54 (36%)
Negative by culture and serology	58 (97%)	51 (94%)
No culture and no serology	1 (2%)	1 (2%)
Negative by culture and no serology	1 (2%)	2 (4%)

Source: NDA 21-246, SE5-017, Clinical Study Report for Protocol WV16193, page 54.
*Defined as positive nasal/throat swab or > 4-fold rise in antibody titers. Type derived from culture and antibody data.

The applicant's analyses showed that the proportion of households with at least one contact case of laboratory-confirmed clinical influenza was significantly less for those in the Prophylaxis group than for those in the No Prophylaxis group. These findings were replicated regardless of which population the applicant evaluated, the ITT, ITTII, or ITTIINAB populations. In these analyses, the applicant estimated the Protective Efficacy as the percentage difference in infection rates between the Prophylaxis and No Prophylaxis groups (ie., 1.0 – Relative Risk) and calculated a Confidence Interval for the effect. These results are summarized in Table 6.1.4B below. The applicant suggests that analysis of the ITTINAB population represents the most accurate assessment of true secondary transmission of influenza within households. Their conclusions regarding the primary endpoint are that Tamiflu given once daily to household contacts of infected index cases provides additional protection against household transmission compared to only treatment of the index cases.

Table 6.1.4B: Number of Households with Contact Cases of Febrile, Laboratory-Confirmed Influenza Within 10 Days of Index Case Start of Treatment – Primary Endpoint Analyses

Study Population	Prophylaxis	No Prophylaxis	
ITT – All households	135	136	Protective Efficacy: 62.7%
No Infected Contacts	125 (93%)	109 (80%)	95% CI: (26.0, 81.2)%
$\geq$ 1 Infected Contact	10 (7%)	27 (20%)	P value: 0.0042
ITTII – All households	84	89	Protective Efficacy: 58.5%
No Infected Contacts	75 (89%)	66 (74%)	95% CI: (15.6, 79.6)%
$\geq$ 1 Infected Contact	9 (11%)	23 (26%)	P value: 0.0114
ITTIINAB – All households	84	89	Protective Efficacy: 78.8%
No Infected Contacts	80 (95%)	69 (78%)	95% CI: (40.6, 92.4)%
$\geq$ 1 Infected Contact	4 (5%)	20 (22%)	P value: 0.0008

Source: NDA 21-246, SE5-017, Clinical Study Report for Protocol WV16193, pages 57 and 248.

In his analysis of the primary endpoint, the FDA Statistical Reviewer evaluated the proportion of households with confirmed influenza in at least one contact in households with a confirmed infected index case. Using the ITTII population, 11% of households in the Prophylaxis group experienced transmission of laboratory confirmed clinical influenza compared to 26% in the No Prophylaxis group (difference 15.1%, 95% CI (3.9, 26.4), P=0.0084). Using the ITTIINAB population, 5% of households in the Prophylaxis group experienced transmission of laboratory confirmed clinical influenza compared to 22% in the No Prophylaxis group (difference 17.7%, 95% CI (7.9, 27.5), P=0.0004). The findings were similar when the analysis included households without an infected index case or all households regardless of which contact population was analyzed. The FDA's independent analysis and the applicant's analysis are very similar and the conclusions regarding the benefit of contact prophylaxis are the same.

One of the applicant's major secondary efficacy analyses was an evaluation of the incidence of influenza infection in individual contacts. The results of these analyses were similar to the analyses focused on households. These analyses showed that the proportion of individual contacts with laboratory-confirmed clinical influenza was significantly less for those in the Prophylaxis group than for those in the No Prophylaxis group. These findings were replicated regardless of which population the applicant evaluated, the ITT, ITTII, or ITTIINAB populations (see Table 6.1.4C). This analysis does not take into consideration the potential of risk interactions among contacts within the same household exposed to the same index case. It is likely, however, that influenza events among contacts within a household are not statistically independent.

Table 6.1.4C: Number of Individual Contact Cases of Febrile, Laboratory-Confirmed Influenza Within 10 Days of Index Case Start of Treatment

Study Population	Prophylaxis	No Prophylaxis	
ITT – All contacts	400	392	Protective Efficacy: 73.1%
No Infected Contacts	389 (97%)	352 (90%)	95% CI: (47.1, 86.3)%
$\geq$ 1 Infected Contact	11 (3%)	40 (10%)	P value: 0.0001
ITTII – All contacts	244	258	Protective Efficacy: 68.0%
No Infected Contacts	234 (96%)	225 (87%)	95% CI: (34.9, 84.2)%
$\geq$ 1 Infected Contact	10 (4%)	33 (13%)	P value: 0.0017
ITTIINAB – All contacts	228	248	Protective Efficacy: 84.5%
No Infected Contacts	224 (98%)	220 (89%)	95% CI: (59.1, 94.1)%
$\geq$ 1 Infected Contact	4 (2%)	28 (11%)	P value: 0.0002

Source: NDA 21-246, SE5-017, Clinical Study Report for Protocol WV16193, pages 58, 59, and 250.

Although the primary endpoint of the study evaluated the development of laboratory-confirmed influenza with clinical symptoms of fever $\geq$ 37.8^{o}C and cough and/or coryza, influenza can present with lesser symptoms or can be asymptomatic. The applicant also evaluated the occurrence of all laboratory-confirmed influenza infection according to household or individual contacts. Their analyses showed that the incidence of any laboratory-confirmed influenza

infection among households were not statistically different between Prophylaxis and No Prophylaxis groups. However, there were significantly fewer contacts in the Prophylaxis group who developed any laboratory-confirmed influenza than in the No Prophylaxis group. These results are summarized in Table 6.1.4D.

Table 6.1.4D: Number of Households and Individual Contact Cases with Any Laboratory-Confirmed Influenza Within 30 Day Study Period

Study Population	Prophylaxis	No Prophylaxis	
ITTII – All households	84	89	Protective Efficacy: 16.6%
No Infected Contacts	47	42	95% CI: (-13.8, 38.9)%
≥ 1 Infected Contact	37	47	P value: 0.2877
ITTII – All contacts	244	258	Protective Efficacy: 35.1%
No Infected Contacts	198	183	95% CI: (8.5, 54.0)%
≥ 1 Infected Contact	46	75	P value: 0.0137

Source: NDA 21-246, SE5-017, Clinical Study Report for Protocol WV16193, pages 69 and 270.

Other secondary efficacy endpoints in the applicant's analysis focused on the length and severity of influenza illness in households or individuals. According to their analysis, the duration of fever and cough/coryza among ITTII contacts who developed confirmed, clinical influenza was significantly shorter for subjects receiving Prophylaxis (mean 20 hours, median 3 hours) than in those receiving No Prophylaxis (mean 58 hours, median 40 hours). The applicant also calculated that significantly fewer households experiencing confirmed, clinical influenza in the Prophylaxis group had contacts that were ill enough to remain in bed compared to households in the No Prophylaxis group (11% vs. 34%). Similarly, the number of individual contacts with confirmed, clinical influenza who were bed-bound was lower in the Prophylaxis group than in the No Prophylaxis group (9% vs. 29%). The rates of pre-defined secondary complications of influenza (bronchitis, pneumonia, otitis media, sinusitis, and lower respiratory tract infection) were low and similar in both treatment groups; 3 in contacts receiving Prophylaxis and 4 in those receiving No Prophylaxis. The applicant notes that the cases of bronchitis (1) and pneumonia (2) were reported only in contacts in the No Prophylaxis group but the numbers of events were too small to draw conclusions. Finally, the applicant analyzed the duration and severity of illness in index cases as parameters that might have implications for transmission within their households (ie., sicker index cases might be more effective transmitters). Index cases in the households receiving Prophylaxis had slightly longer duration of illness and greater severity (as measured by AUC of cough and coryza scores) of symptoms than did those in households receiving No Prophylaxis. Although quantitative viral cultures were not performed, this suggests that the greater proportion of ill households and contacts in the No Prophylaxis group was not due to lower index case risk for household transmission.

The FDA Statistical Reviewer also independently evaluated some of the secondary efficacy endpoints. He confirmed the applicant's conclusions regarding the proportion of contacts with confirmed, clinical influenza in households with a confirmed infected index case. Using the

ITTII population, 4% of contacts in the Prophylaxis group experienced transmission of laboratory confirmed clinical influenza compared to 13% in the No Prophylaxis group (difference 8.7%, 95% CI (3.9, 13.5), P=0.0004). Using the ITTIINAB population, 2% of contacts in the Prophylaxis group experienced transmission of laboratory confirmed clinical influenza compared to 11% in the No Prophylaxis group (difference 9.5%, 95% CI (5.2, 13.8), P<0.0001). The FDA evaluation of households and contacts with any laboratory-confirmed influenza also showed no statistical difference between treatment groups in the proportion of households with any confirmed influenza but significantly lower incidence of individual contacts with any confirmed influenza in the Prophylaxis group.

The FDA analysis also confirmed that Tamiflu prophylaxis appeared to reduce the duration of influenza illness in subjects with laboratory-confirmed, clinical influenza. Duration of illness in both households and individual contacts was significantly shorter among those receiving Prophylaxis than in those receiving No Prophylaxis.

Analysis of efficacy according to a variety of demographic factors was performed by the FDA Statistical Reviewer. The effect of prophylaxis was consistent across genders, races, and age categories. Some categories (Asian race, age 1 to 4 years) in which there were too few subjects to draw meaningful conclusions. The benefits of prophylaxis were apparent regardless of whether the endpoint evaluated was confirmed, clinical influenza or all laboratory-confirmed influenza infection.

Subgroup Analysis: Efficacy in Pediatric Patients 1 to 12 Years of Age

The primary purpose of this efficacy supplement is to support the prophylaxis indication for Tamiflu in pediatric patients 1 to 12 years of age. To this end, the applicant provided a subgroup analysis of efficacy in this age group. The applicant identified 134 index cases 1-12 years of age and 222 contacts in this age group. Their ITT population in this age group includes 215 contacts; 3 contacts excluded because they "did not receive oseltamivir and were excluded from the safety population", 3 contacts excluded who had no efficacy data collected, and one excluded who had only partial efficacy data.

The applicant used similar study populations in the pediatric age group as were used in the study's primary efficacy analysis. Their results indicate that the use of Tamiflu prophylaxis in patients 1 to 12 years of age provided similar benefit compared to its use in adults and adolescents. Pediatric contacts in the Prophylaxis group were less likely to acquire laboratory-confirmed clinical influenza than pediatric contacts receiving No Prophylaxis. The results of these analyses are summarized in Table 6.1.4E. The FDA Statistical Reviewer was able to confirm this subgroup analysis and agreed with the conclusions.

Table 6.1.4E: Number of Contact Cases 1-12 Years of Age with Febrile, Laboratory-Confirmed Influenza Within 10 Days of Index Case Start of Treatment

Population	Prophylaxis (Number infected/Total)	No Prophylaxis (Number infected/Total)	Protective Efficacy % (95% CI)	P-value
ITT	7/104 (7%)	21/111 (19%)	64.4 (15.8, 85.0)	0.0188
ITTII	6/55 (11%)	18/74 (24%)	55.2 (-13.0, 82.2)	0.089
ITTIINAB	2/47 (4%)	15/70 (21%)	80.1 (22.0, 94.9)	0.0206

Source: NDA 21-246, SE5-017, Benefit Risk Summary for Use of Tamiflu in Pediatric Prophylaxis, page 15.

In addition to the analyses reported above, the Statistical Reviewer evaluated the proportions of contacts not shedding influenza virus at baseline who developed confirmed, clinical influenza regardless of the infection status of the index case. This allows some assessment of the effect of prophylaxis on community-acquired influenza (non-household) in this population. When this population is analyzed, the incidence of confirmed, clinical influenza was decreased from 17% in contacts receiving No Prophylaxis to 3% in those receiving Tamiflu QD (P=0.0006). This analysis will be displayed in the revised Tamiflu label as it provides the broadest, most appropriate population showing significant benefit from prophylaxis.

The efficacy results were most significant for patients in the age range 6 to 12 years. Slightly fewer than 25% of the pediatric contacts were 1 to 5 years of age and the numbers enrolled in the younger ages were not sufficient to establish efficacy in that subgroup of younger patients. It is known that younger children may shed influenza virus for longer periods than older children and adults and may have higher rates of influenza-related morbidity. It is not anticipated that these events or other pathophysiologic processes would make them less likely to benefit from prophylaxis.

6.1.5 Clinical Microbiology

The study reported in this supplement used a combination of influenza virus culture and influenza serology as a component of the primary endpoint and several secondary endpoints. Laboratory confirmation of influenza as the cause of the clinical illness required either detection of viral shedding within 2 days before or after reported fever or a $\geq$ 4-fold increase in influenza-specific antibody levels between baseline and study Day 30. All influenza virus isolates from index cases and ill contacts were identified by strain type so that index case strains could be compared to those of the contacts in their households. As noted in Table 6.1.4A, only a small number of index cases (5) did not have both culture and serology data. The predominant strains identified among study participants were influenza A H1N1 and influenza B, with a small number of participants infected with influenza A H3N2.

The applicant did a limited analysis of the incidence of viral shedding among contacts who developed influenza. They note that among those contacts in the ITTIINAB population, there was significantly lower incidence of detectable shedding of influenza virus in contacts receiving Prophylaxis compared to those receiving No Prophylaxis (0 vs. 7%). Among households with infected index cases, a total of 16 contacts receiving Prophylaxis and 10 receiving No Prophylaxis were actively shedding virus at the time of study entry. The applicant identified that contacts were predominantly infected with influenza strains that were concordant with the strain of the household index case, but 23/74 typed strains (31%) in contact cases of influenza were discordant with the index case.

Analysis of the susceptibility of the study isolates' neuraminidase to Tamiflu was evaluated for all infected participants. No isolates with reduced susceptibility were identified. The applicant concludes that there was no evidence for generation of resistant influenza virus among treated study subjects or transmission of resistant virus within households.

6.1.6 Efficacy Conclusions

Based on the results of Study WV16193, the applicant concluded that Tamiflu administered once daily as prophylaxis was effective in limiting household transmission among exposed contacts when they were provided prophylaxis for 10 days beginning within 48 hours of identification and start of treatment of the index case. The design of this study allowed confirmation that there was additional benefit in the use of prophylaxis above that of only treating the ill index case in the household. The benefit of prophylaxis was shown in both adults and adolescents $\geq$ 13 years of age, the group for whom Tamiflu is currently indicated for prophylaxis, and in household contacts 1 to 12 years of age. The applicant provided multiple secondary analyses using different study populations, all of which were consistent with their conclusions. A secondary analysis evaluating the duration of influenza illness documented that among those contacts who developed clinical influenza, those who received Tamiflu prophylaxis were ill for a shorter period of time. Additionally, the applicant concluded that there was no evidence that Tamiflu-resistant influenza virus was generated or transmitted within households or emerged among those contacts who developed influenza in spite of receiving prophylaxis.

Independent FDA statistical analysis of the study data confirmed the applicant's findings and conclusions. The risk of at least one new contact (not shedding influenza virus at baseline) per household developing laboratory-confirmed, clinical influenza in the setting of confirmed infection in the index case was reduced from 22% in households not receiving prophylaxis to 5% in those receiving Tamiflu once daily for 10 days (P=0.0004). Similarly, the risk of confirmed, clinical influenza among individual contacts not already shedding influenza virus at baseline was reduced from 11% in those contacts not receiving prophylaxis to 2% in those receiving Tamiflu (P<0.0001). In sensitivity analyses, the benefit of prophylaxis was confirmed regardless of the infection status of the index case or the baseline infection status of the contacts. Finally, if all confirmed influenza infections (symptomatic and asymptomatic) were evaluated, the proportion of contacts developing influenza was significantly reduced in those contacts receiving prophylaxis and the proportion of households with at least one new case of influenza trended the same direction but did not reach significance. The FDA statistical analysis also confirmed that

the duration of influenza illness appeared to be shorter in those contacts who developed influenza while receiving prophylaxis compared to those who did not receive prophylaxis.

The benefit of prophylaxis was apparent in the age subgroup targeted in this submission, pediatric patients 1 to 12 years of age. In this subgroup, the proportion of contacts not shedding influenza virus at baseline who developed confirmed, clinical influenza decreased from 17% in those not receiving prophylaxis to 3% in those receiving prophylaxis (P=0.0006). Although the study was not initially designed to show the benefit of prophylaxis specifically in pediatric patients, this study provides adequate data for assessing the efficacy of household prophylaxis in patients 1-12 years of age.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data for this NDA supplement was provided in the form of electronic datasets containing tabulations of clinical adverse events. Narrative summaries and case report forms were provided for all patients who died, developed serious adverse events (SAEs), or discontinued study drug because of an adverse event (AE). Tabulations of AEs, SAEs, and study drug discontinuations or interruptions were compiled using the JMP Statistical Discovery Software (SAS Institute, Inc).

The safety analysis included all index cases who received at least one dose of study drug, all contact cases in the Prophylaxis group who received at least one dose of study drug, and all contacts in the No Prophylaxis group who were randomized into the study.

7.1.1 Deaths

No deaths were reported in Study WV16193 during either study treatment or follow-up.

7.1.2 Other Serious Adverse Events

A total of 5 SAEs were reported in Study WV16193, 3 in patients receiving Tamiflu and 2 in patients not receiving Tamiflu (after completing treatment as index cases). One of the patients reporting an SAE was in the pediatric age range (17 years). No SAEs were reported in patients who did not receive Tamiflu. Brief summaries of the 5 SAE cases are included below:

- #8107 – This 41 year old female index case was hospitalized on Day 3 of Tamiflu treatment for pneumonia. She had a medical history significant for asthma. The patient presented to the Emergency Room on Day 3 with symptoms of shortness of breath, increased cough, brownish sputum, and back pain. CXR revealed right middle and right lower lobe pneumonia. She was admitted and treated with bronchodilators, antibiotics, and supportive

medications. Study drug was continued. The investigator considered the event unrelated to study medication. This patient had laboratory-confirmed influenza.

- #6851 – This 17 year old female index case was hospitalized on Day 5 for a "nervous breakdown." She had a medical history significant for depression. She was admitted but the narrative summary states that she received no treatment and was discharged on Day 7 with a recommendation to have psychological counseling and support. The patient forgot/missed her last dose of study medication because of the event. The investigator considered the event unrelated to study drug. This patient had laboratory-confirmed influenza.

- #6893 – This 28 year old female household contact receiving Tamiflu prophylaxis was hospitalized for exacerbation of her asthma on study day 6. She had a medical history significant for asthma, allergic rhinitis, hypertension, GERD, obesity, and depression and was receiving multiple medications for these conditions. The patient was admitted and received treatment with bronchodilators. She was discharged on Day 7. Study drug was continued during hospitalization. The investigator considered the event unrelated to study drug. This patient did not have laboratory-confirmed influenza.

- #2402 – This 60 year old female index case was hospitalized on Day 16 for decompensation of cardiac failure. She had a medical history significant for hypertension, COPD, cardiac insufficiency, pedal edema, and stasis dermatitis of the leg. Beginning on Day 10, she experienced worsening of her edema and stasis dermatitis. She was admitted for worsening cardiac failure on Day 16 and was treated with captopril, furosemide, and potassium. She remained hospitalized until Day 37 when the event was considered resolved. The patient had completed her 5 day course of influenza treatment 5 days prior to the beginning of the event symptoms. The investigator considered the event unrelated to study drug. This patient did not have laboratory-confirmed influenza.

- #1603 – This 27 year old male index case was hospitalized for a pleural effusion on Day 10. The patient was also receiving concomitant carbocystein and amoxicillin-clavulanate. On Day 9 laboratory studies revealed a C-reactive protein of 151 mg/L (high). On Day 10 he developed a fever and a CXR revealed a right pleural effusion. The patient was hospitalized and a thoracentesis was performed. On Day 15 the patient began receiving isoniazid, rifampicin, and ethambutol. A thoracoscopic biopsy performed on Day 17 identified tuberculosis. The patient had completed his 5 day course of influenza treatment 5 days before the event. The investigator considered the event unrelated to study drug. This patient did not have laboratory-confirmed influenza.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The study report identifies 28 subjects (3%) who withdrew from the study prematurely. The applicant provided case summaries for those patients who discontinued study prematurely because of an AE and these cases will be described in the next section. Table 7.1.3.1A summarizes the reasons for premature withdrawal from the study as described by the applicant.

Table 7.1.3.1A: Summary of Reasons for Premature Withdrawal from Study 16193 – All Randomized Subjects

Reason for Withdrawal	Index Cases (N=298)	Contacts Prophylaxis Group (N=410)	Contacts No Prophylaxis Group (N=402)
Withdrew for any reason	8 (3%)	7 (2%)	13 (3%)
Refused treatment, withdrew consent, did not cooperate	2 (<1%)	6 (1%)	4 (1%)
Failed to return	3 (1%)	0	8 (2%)
Adverse events	3 (1%)	1 (<1%)	1 (<1%)

Source: NDA 21-246, SE5-017, Clinical Study Report for Protocol WV16193, page 50.

7.1.3.2 Adverse events associated with dropouts

Only 5 of 1110 randomized subjects prematurely discontinued study drug in Study WV16193. Brief narratives of these events are summarized below. None of the patients who prematurely discontinued study drug because of AEs were noted to have any sequelae from the events.

- #1125 – This 36 year old male contact was enrolled in the study in the No Prophylaxis group. He was diagnosed with clinical influenza on study Day 3 and began treatment with Tamiflu 75 mg BID on that day. He developed an allergic/hypersensitivity reaction of moderate severity on study Day 4 and discontinued Tamiflu on study Day 6 after receiving 6 doses of study drug. The adverse reaction was treated with Tavegil and prednisolone and the event resolved on study Day 12. The event was considered probably related to study drug. His influenza was laboratory-confirmed.

- #1137 – This 66 year old female index case received initial treatment with Tamiflu 75 mg BID. She discontinued study drug on study Day 4 after 6 doses because of moderate nausea and the event resolved within 2 days. The event was considered probably related to study drug. This patient had laboratory-confirmed influenza.

- #1814 – This 8 year old male contact was enrolled in the Prophylaxis group and received Tamiflu 60 mg QD. He experienced 2 episodes of vomiting after taking study drug on Days 7 and 8. The vomiting was described as mild. Study drug was discontinued on Day 8 after 8 doses and the event resolved the same day. The events were considered possibly related to study drug. This patient had laboratory-confirmed influenza but was not diagnosed with clinical influenza.

- #1839 – This 14 year old male index case received initial treatment with Tamiflu 75 mg BID. He had mild vomiting on study Day 1 for one day. On study Day 2 he experienced mild epistaxis and discontinued Tamiflu after 3 doses of study drug. The event resolved the same day. These events were considered possibly related to study drug. This patient had laboratory-confirmed influenza.

- #4102 – This 6 year old male index case received initial treatment with Tamiflu 60 mg BID. He experienced episodes of severe nausea and moderate vomiting on Day 1, resolving on Day 5. He missed one dose of study drug on Day 3 and stopped taking Tamiflu on Day 5 after receiving 7 doses. These events were considered probably related to study drug. This patient did not have laboratory-confirmed influenza.

7.1.3.3 Other significant adverse events

Neuropsychiatric AEs and serious skin/hypersensitivity reactions were evaluated as part of a pediatric safety update (see Section 7.1.4). No other significant AEs were evaluated.

7.1.4 Other Search Strategies

As part of a post-marketing safety review of Tamiflu use in pediatric patients mandated by the Best Pharmaceuticals for Children Act, clinical neuropsychiatric AEs and skin/hypersensitivity reactions were evaluated in more detail. These types of events were given special attention because they represented the major categories of AEs spontaneously reported to the FDA's Adverse Event Reporting System. The data from Study WV16193 and the previously-reviewed pediatric Tamiflu treatment trials were used to provide context for the AERS safety data.

Patients from 1 to 18 years of age were selected from the study database and evaluated for selected clinical AEs including neurologic/psychiatric events and severe skin/hypersensitivity events. A total of 534 patients 1 to 18 years of age enrolled in Study WV16193, 181 as index cases and 353 as contacts. Of the pediatric patients enrolled, 143 received no treatment with Tamiflu, 168 received Tamiflu QD prophylaxis, 212 received Tamiflu BID as treatment, and 11 received both some QD prophylaxis and BID treatment. The 1-18 year age range was used to provide the most inclusive evaluation of pediatric patients. Tablet 7.1.4A summarizes the total number of patients 1 to 18 years of age with reported AEs in different body system categories.

Table 7.1.4A: Pediatric Clinical Adverse Events According to Body System Category – Study WV16193

AE Body System Category	Tamiflu QD (N=168)	Tamiflu BID (N=212)	Tamiflu QD+BID (N=11)	No Prophylaxis (N=143)
Disorders of blood and lymphatic system	0	1	0	0
Disorders of metabolism and nutrition	1	3 (1%)	0	0
Disorders of the ear and labyrinth	1	2	1 (9%)	0
Disorders of the eye	1	0	0	2(1%)
Gastrointestinal disorders	32 (19%)	49 (23%)	2 (18%)	3 (2%)
General disorders	15 (9%)	12 (6%)	0	25 (17%)
Infections and infestations	20 (12%)	40 (19%)	0	25 (17%)
Injury and poisoning	2	2	0	2 (1%)
Musculoskeletal, connective tissue and bone disorders	0	2	0	1
Neurological disorders	16 (10%)	6 (3%)	0	18 (13%)
Psychiatric disorders	1	1	0	0
Renal and urinary disorders	0	1	0	0
Respiratory, thoracic and mediastinal disorders	51 (30%)	45 (21%)	1 (9%)	51 (36%)
Skin and subcutaneous disorders	1	6 (3%)	0	0
Surgical and medical procedures	1	0	0	0

The combined neurologic and psychiatric (neuropsychiatric) AEs in patients 1 to 18 years of age were evaluated according to Tamiflu treatment received (see Table 7.1.4B). The most common neuropsychiatric AE reported was headache, reported in 3% of pediatric subjects receiving Tamiflu BID, 8% of children receiving Tamiflu QD prophylaxis, and 12% of children receiving No Prophylaxis. The events of "nervous breakdown" and "psychiatric disorder" were reported in adolescent subjects each of whom were noted to have a history of psychiatric symptoms prior to beginning study drug.

Table 7.1.4B: Pediatric Neurologic and Psychiatric Adverse Events – Study WV16193

Clinical AE Preferred Term	Tamiflu QD (N=168)	Tamiflu BID (N=212)	No Prophylaxis (N=143)
Headache NOS	14 (8%)	6 (3%)	17 (12%)
Headache aggravated	1	0	0
Insomnia	1	0	0
Migraine	0	0	1
Nervous breakdown	0	1	0
Psychiatric disorder	1	0	0

NOS, not otherwise specified
No neuropsych AEs were reported among the small number of pediatric patients who received QD+BID dosing of Tamiflu.

The combined serious skin/hypersensitivity AEs in patients 1 to 18 years of age were also evaluated according to Tamiflu treatment received (see Table 7.1.4C). The most common event reported in this category was unspecified dermatitis, reported in 3 subjects receiving Tamiflu BID. Although the number of events is very small, it is of interest that the events of erythema multiforme, urticaria, and periorbital edema occurred only in the Tamiflu BID group.

Table 7.1.4C: Pediatric Skin/Hypersensitivity Adverse Events – Study WV16193

Clinical AE Preferred Term	Tamiflu QD (N=168)	Tamiflu BID (N=212)	No Prophylaxis (N=143)
Dermatitis NOS	0	3	0
Eczema NOS	1	0	0
Erythema multiforme	0	1	0
Periorbital edema	0	1	0
Urticaria NOS	0	1	0

NOS, not otherwise specified
No serious skin/hypersensitivity AEs were reported among the small number of pediatric patients who received QD+BID dosing of Tamiflu.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were recorded at each of the study visits. In addition to solicitation of AEs by study staff at clinic or home visits, study participants could also use the diary cards to record AEs

between study visits. It should be noted that for subjects who received Tamiflu BID for treatment of influenza, cough and nasal congestion (coryza) were reported as symptoms of illness and were recorded as efficacy measures but were not recorded as AEs. In subjects receiving Tamiflu QD or No Prophylaxis, who were not considered to have clinical influenza, these events were recorded as AEs and graded for severity.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor used the MedDRA Version 1.5 dictionary for classifying AEs by body system category and preferred terms. This was an accepted classification system for use in clinical trials at the time this study was conducted, although it has since been updated. The electronic dataset also contains the original verbatim terminology used by the investigator to describe the event. AEs were graded for severity from 1 (mild) to 4 (severe/life threatening) according to the WHO grading scale that was included in the protocol.

7.1.5.3 Incidence of common adverse events

The applicant analyzed the safety data for index case patients and household contacts separately. The primary safety analysis comparison was between the contacts who received Tamiflu QD in the Prophylaxis groups and those who received No Prophylaxis but became ill and received Tamiflu BID. The applicant did not include in the safety analysis the contacts randomized to the No Prophylaxis group who never received Tamiflu although that group provides a very useful control for this large population of people interacting as households. The applicant focused their analysis on the "on treatment" period that begins with the first dose of study drug and extends until 2 days after the last dose of study drug.

The applicant notes in their analysis of all on-treatment AEs, a higher incidence of AEs was reported by contacts in the Prophylaxis group (45%) than by those in the No Prophylaxis but treated group (31%) or the Index Case group (30%). Among the contacts, the most commonly reported AEs were in the respiratory, gastrointestinal, and general disorders. The most commonly reported individual AEs in subjects in the Prophylaxis group were: nasal congestion (11%), cough (7%), sore throat (5%), nausea (8%), vomiting (5%), fatigue (6%), pain (4%), nasopharyngitis (4%), and headache (8%). Among contacts who received Tamiflu BID treatment the most commonly reported AEs included: vomiting (10%), diarrhea (4%), nausea (2%), and nasal congestion (2%). Many of the specific AEs reported during the on-treatment period are events commonly experienced by people with influenza or other winter/seasonal viral illnesses. The applicant notes that the incidence of vomiting was greater among those subjects receiving treatment with Tamiflu (10%) than in those receiving prophylaxis (5%).

This reviewer analyzed the safety data using 4 treatment groups defined by the actual study regimen received. In evaluating the incidence of AEs in this study it is important to consider that some patients received study drug while others did not and that some patients developed clinical influenza while others did not. Subjects in the review safety group "Tamiflu QD" included contacts who received Tamiflu QD prophylaxis and were never treated for clinical influenza. Likewise, those in the "No Prophylaxis" group received no prophylaxis and were never treated

for clinical influenza (ie., never received Tamiflu). Patients in the groups "Tamiflu BID" and "Tamiflu QD + BID" included those subjects who received a treatment course of Tamiflu (either index cases or contacts) and those who received both some prophylaxis and treatment. All patients in these 2 groups received study drug but also had clinical symptoms consistent with influenza. The assessment that best compares potential toxicity of study drug without the confounding presence of clinical influenza is the comparison of the Tamiflu QD group to the No Prophylaxis group. The reviewer's safety analysis included both the entire study period and the on-treatment period.

The most commonly reported AEs among patients receiving Tamiflu either as treatment or prophylaxis were respiratory disorders, gastrointestinal disorders, infections/infestations, general disorders, and neurologic disorders. Comparing the Tamiflu QD group to the No Prophylaxis group identified that cough (11% vs. 16%), fatigue (9% vs. 16%), headache (11% vs. 16%), and nasal congestion (14% vs. 19%) were reported at slightly higher rates in those subjects who did not receive Tamiflu. Clearly, these are events that might represent symptoms of influenza or other seasonal viral infections. Events such as nausea and vomiting were observed in more of the Tamiflu QD group (9% and 5%, respectively) than in the No Prophylaxis group (<1% each). Comparing the Tamiflu QD group to the Tamiflu BID group confirmed the applicant's conclusion that there was a higher incidence of vomiting among subjects receiving Tamiflu treatment (10%) compared to prophylaxis (5%).

A summary of reported AEs through the entire study period by body system category is shown in Table 7.1.5.3A. Specific AEs reported in > 2% of any treatment group (except the small Tamiflu QD + BID group) for the entire study period are summarized in Table 7.1.5.3B. The Tamiflu QD and No Prophylaxis groups are highlighted to facilitate comparison of the 2 groups of subjects who did not have diagnosed clinical influenza as a confounding event. Based on the virologic and serologic data available it is likely that some of the subjects in both of these groups had subclinical or unrecognized influenza or other seasonal viral infection.

Table 7.1.5.3A: All Adverse Events Reported by Body System Category, All Ages

AE Body System Category	Tamiflu QD (N=399)	Tamiflu BID (N=347)	Tamiflu QD+BID (N=17)	No Prophylaxis (N=345)
Cardiac disorders	1 (<1%)	1 (<1%)	0	0
Disorders of blood and lymphatic system	0	1 (<1%)	0	0
Disorders of metabolism and nutrition	3 (<1%)	3 (<1%)	0	0
Disorders of the ear and labyrinth	1 (<1%)	4 (1%)	1 (6%)	1 (<1%)
Disorders of the eye	2 (<1%)	0	0	2 (<1%)
Disorders of the immune system	1 (<1%)	1 (<1%)		1 (<1%)

Disorders of the reproductive system and breast	1 (<1%)	0	0	0
Endocrine disorders	0	1 (<1%)	0	0
Gastrointestinal disorders	70 (18%)	66 (19%)	2 (12%)	6 (2%)
General disorders	58 (15%)	23 (7%)	0	76 (22%)
Infections and infestations	50 (13%)	66 (19%)	1 (6%)	66 (19%)
Injury and poisoning	3 (<1%)	2 (<1%)	0	6 (2%)
Musculoskeletal, connective tissue and bone disorders	7 (2%)	3 (<1%)	0	6 (2%)
Neurological disorders	55 (14%)	21 (6%)	0	59 (17%)
Pregnancy, puerperium, and perinatal conditions	0	0	0	1 (<1%)
Psychiatric disorders	2 (<1%)	2 (<1%)	0	0
Renal and urinary disorders	1 (<1%)	2 (<1%)	0	0
Respiratory, thoracic and mediastinal disorders	94 (24%)	64 (18%)	1 (6%)	99 (29%)
Skin and subcutaneous disorders	1 (<1%)	6 (2%)	0	1 (<1%)
Surgical and medical procedures	1 (<1%)	0	0	1 (<1%)

Table 7.1.5.3B: All Reported Adverse Events Occurring in > 2% of Any Treatment Group, All Ages

Clinical AE Preferred Term	Tamiflu QD (N=399)	Tamiflu BID (N=347)	Tamiflu QD+BID (N=17)	No Prophylaxis (N=345)
Any reported AE	210 (53%)	172 (50%)	3 (18%)	182 (53%)
Abdominal pain, upper	6 (2%)	6 (2%)	1 (6%)	1 (< 1%)
Bronchitis NOS	3 (< 1%)	8 (2%)	0	7 (2%)
Cough	42 (11%)	27 (8%)	1 (6%)	56 (16%)
Diarrhea NOS	4 (1%)	10 (3%)	0	2 (< 1%)
Fatigue	35 (9%)	7 (2%)	0	56 (16%)
Headache NOS	45 (11%)	20 (6%)	0	56 (16%)
Nasal congestion	57 (14%)	26 (7%)	1 (6%)	65 (19%)
Nasopharyngitis	22 (6%)	12 (3%)	1 (6%)	26 (8%)
Nausea	35 (9%)	25 (7%)	0	2 (< 1%)
Pain NOS	24 (6%)	6 (2%)	0	31 (9%)
Pyrexia	14 (4%)	7(2%)	0	19 (6%)
Rhinitis allergic NOS	7 (2%)	10 (3%)	0	8 (2%)
Sore throat NOS	28 (7%)	15 (4%)	0	34 (10%)

Upper respiratory tract infection NOS	7 (2%)	7 (2%)	0	10 (3%)
Vomiting NOS	21 (5%)	35 (10%)	2 (12%)	3 (< 1%)

NOS, not otherwise specified

Since the submission focuses on the use of Tamiflu prophylaxis in pediatric patients 1 to 12 years of age, this age group was evaluated separately (see Table 7.1.5.3C). Over the entire study period, subjects 1 to 12 years of age reported higher rates of cough, nasal congestion, and vomiting than were reported by the full study population. The rates of cough and nasal congestion in children receiving Tamiflu QD (23% and 22%, respectively) were similar to those in children receiving No Prophylaxis (25% and 18%). As in the full study population, the rate of vomiting appeared to be dose-related and was highest in children receiving Tamiflu BID and lowest in those receiving No Prophylaxis.

Table 7.1.5.3C: All Reported Adverse Events Occurring in > 2% of Any Treatment Group, Subjects 1 through 12 Years of Age

Clinical AE Preferred Term	Tamiflu QD (N=99)	Tamiflu BID (N=158)	Tamiflu QD+BID (N=7)	No Prophylaxis (N=92)
Any reported AE	60 (61%)	92 (58%)	2 (29%)	46 (50%)
Abdominal pain, upper	1 (1%)	3 (2%)	1 (14%)	0
Bronchitis NOS	0	3 (2%)	0	2 (2%)
Cough	23 (23%)	16 (10%)	1 (14%)	23 (25%)
Dermatitis NOS	0	3 (2%)	0	0
Diarrhea NOS	1 (1%)	6 (4%)	0	0
Dyspepsia	3 (3%)	1 (<1%)	0	0
Ear infection NOS	1 (1%)	4 (3%)	0	0
Epistaxis	1 (1%)	3 (2%)	0	0
Headache NOS	7 (7%)	2 (1%)	0	1 (1%)
Nasal congestion	22 (22%)	12 (8%)	1 (14%)	17 (18%)
Nasopharyngitis	2 (2%)	6 (4%)	0	4 (4%)
Nausea	4 (4%)	10 (6%)	0	1 (1%)
Otitis media NOS	4 (4%)	3 (2%)	0	2 (2%)
Pharyngitis streptococcal	1 (1%)	3 (2%)	0	0
Pyrexia	4 (4%)	4 (3%)	0	6 (7%)
Rhinitis allergic NOS	2 (2%)	7 (4%)	0	1 (1%)
Rhinorrhea	3 (3%)	2 (1%)	0	1 (1%)
Sore throat NOS	0	4 (3%)	0	1 (1%)
Upper respiratory tract infection NOS	2 (2%)	2 (1%)	0	3 (3%)
Vomiting NOS	12 (12%)	31 (20%)	2 (29%)	2 (2%)

NOS, not otherwise specified

7.1.5.4 Common adverse event tables

The rates of common AEs were also evaluated in the study safety population for just the on-treatment period. Summary tables of this analysis will be incorporated into the Tamiflu label safety display for both adult/adolescent subjects and children 1 to 12 years of age. In this evaluation, AEs were tabulated for the duration of dosing of study drug plus 2 days: a total of 12 days for patients receiving Tamiflu QD prophylaxis, 7 days for those receiving Tamiflu BID treatment, and a variable length for those receiving both some prophylaxis and a course of treatment. As is reported by the applicant, the group receiving Tamiflu QD had higher rates of cough (7%), headache (8%), nasal congestion (11%), fatigue (6%), and sore throat (5%), while those receiving Tamiflu BID had higher rates of vomiting (10%). The applicant speculated that the higher rates of some AEs in the Tamiflu QD group were due to the longer reporting period for those subjects and because subjects who received Tamiflu BID for treatment of influenza reported cough and nasal congestion (coryza) as symptoms of illness but not as AEs.

Table 7.1.5.4A: Adverse Events Reported in > 1% of Any Treatment Group – On Treatment, All Ages *

Clinical AE Preferred Term	Tamiflu QD (N=399)	Tamiflu BID (N=347)	Tamiflu QD+BID (N=17)
Any reported AE	181 (45%)	106 (31%)	2 (12%)
Abdominal pain, upper	6 (2%)	5 (1%)	0
Cough	29 (7%)	7 (2%)	1 (6%)
Diarrhea NOS	3 (<1%)	7 (2%)	0
Dyspepsia	6 (2%)	1 (<1%)	0
Fatigue	22 (6%)	1 (<1%)	0
Headache NOS	31 (8%)	5 (1%)	0
Loose stools	5 (1%)	0	0
Nasal congestion	44 (11%)	10 (3%)	1 (6%)
Nasopharyngitis	17 (4%)	0	1 (6%)
Nausea	33 (8%)	24 (7%)	0
Pain NOS	17 (4%)	2 (<1%)	0
Pyrexia	7 (2%)	0	0
Rhinitis allergic NOS	5 (1%)	2 (<1%)	0
Sore throat NOS	18 (5%)	3 (<1%)	0
Vomiting NOS	18 (5%)	35 (10%)	1 (6%)

*An on treatment AE was defined as occurring while on study drug or within 2 days of completing drug.
NOS, not otherwise specified

The rates of on-treatment AEs in study subjects 1 to 12 years of age were evaluated as a safety subgroup. Table 7.1.5.4B displays the on-treatment AEs occurring in > 1% of children 1 to 12

years of age. The data for the QD and BID regimens will be incorporated into the pediatric safety table in the Tamiflu label as representative of the prophylaxis and treatment dosing regimens used in this study. No other safety data is available in pediatric patients receiving Tamiflu prophylaxis. As noted for the full study period, rates of cough and nasal congestion were higher in children receiving Tamiflu QD (18% and 16%, respectively) and rates of vomiting were higher in children receiving Tamiflu BID (20%) and were higher than those reported in the full study population. As was observed in the previously-reviewed Tamiflu treatment trials, children receiving Tamiflu were noted to have higher rates of vomiting than adults.

Table 7.1.5.4B: All Reported Adverse Events in > 1% of Any Treatment Group –On Treatment, Subjects 1 through 12 Years of Age,*

Clinical AE Preferred Term	Tamiflu QD (N=99)	Tamiflu BID (N=158)	Tamiflu QD+BID (N=7)
Any reported AE	51 (52%)	59 (37%)	1 (14%)
Abdominal pain	3 (3%)	3 (2%)	0
Bronchitis NOS	0	3 (2%)	0
Cough	18 (18%)	4 (3%)	1 (14%)
Diarrhea NOS	1 (1%)	5 (3%)	0
Dyspepsia	3 (3%)	1 (<1%)	0
Headache NOS	5 (5%)	0	0
Nasal congestion	16 (16%)	3 (2%)	1 (14%)
Nausea	4 (4%)	10 (6%)	0
Pyrexia	3 (3%)	0	0
Vomiting NOS	10 (10%)	31 (20%)	1 (14%)

*An on treatment AE was defined as occurring while on study drug or within 2 days of completing drug.
NOS, not otherwise specified

7.1.5.5 Identifying common and drug-related adverse events

The AE reporting for study WV16193 required that the local investigators assign each AE a relationship to study drug (unrelated, remotely related, possibly related, probably related). This designation is of limited value in studies like this one that are not blinded and some subjects are known to be receiving no study drug. Five (1%) subjects receiving No Prophylaxis reported an AE considered by the investigator to be remotely, possibly, or probably related to study drug. A total of 78 (20%) subjects receiving Tamiflu QD and 75 (22%) subjects receiving Tamiflu BID reported AEs that were considered study drug related. Most of the events considered drug-related were gastrointestinal events as shown in Table 7.1.5.5A.

Table 7.1.5.5A: All Adverse Events Considered Remotely, Possibly, or Probably Related to Study Drug, All Ages

Clinical AE Preferred Term	Tamiflu QD (N=399)	Tamiflu BID (N=347)	Tamiflu QD+BID (N=17)	No Prophylaxis (N=345)
Any drug-related AE	78 (20%)	75 (22%)	1 (6%)	5 (1%)
Abdominal pain, upper	6 (2%)	5 (1%)	0	0
Diarrhea NOS	3 (<1%)	6 (2%)	0	0
Dyspepsia	6 (2%)	1 (<1%)	0	0
Fatigue	6 (2%)	0	0	2 (<1%)
Headache NOS	12 (3%)	3 (<1%)	0	1 (<1%)
Insomnia	3 (<1%)	0	0	0
Loose stools	4 (1%)	0	0	0
Nasal congestion	8 (2%)	4 (1%)	0	0
Nausea	31 (8%)	22 (6%)	0	1 (<1%)
Sedation	3 (<1%)	0	0	0
Sore throat NOS	3 (<1%)	3 (<1%)	0	2 (<1%)
Vomiting NOS	17 (4%)	34 (10%)	1 (6%)	1 (<1%)

NOS, not otherwise specified

Most of the AEs reported during the study were considered mild in severity and unrelated to study drug. Events that were of moderate severity and considered related to study drug were uncommon and are tabulated by treatment received in Table 7.1.5.5B. Vomiting was the AE most frequently reported to be at least moderate in severity and drug-related. As noted in Section 7.1.3.1, 3 patients discontinued study drug because of AEs that were of moderate severity and thought to be related to study drug.

Table 7.1.5.5B: Adverse Events of at least Moderate Severity Considered Remotely, Possibly, or Probably Related to Study Drug, All Ages

Clinical AE Preferred Term	Tamiflu QD (N=399)	Tamiflu BID (N=347)	Tamiflu QD+BID (N=17)	No Prophylaxis (N=345)
Abdominal pain, upper	4 (1%)	2 (<1%)	0	0
Fatigue	3 (<1%)	0	0	1 (<1%)
Headache NOS	4 (1%)	3 (<1%)	0	0
Loose stools	3 (<1%)	0	0	0
Nausea	7 (2%)	7 (2%)	0	1 (<1%)
Vomiting NOS	3 (<1%)	12 (3%)	1 (6%)	1 (<1%)

NOS, not otherwise specified

7.1.5.6 Additional analyses and explorations

No additional analyses of drug-related adverse events were performed for this supplement.

7.1.6 Less Common Adverse Events

Because the database for this single-study submission was relatively small, no additional analyses to evaluate for less common adverse events were performed.

7.1.7 Laboratory Findings

Since Tamiflu was previously approved for use in treatment of influenza in patients > 1 year of age and for prophylaxis in patients ≥ 13 years of age, it was not considered necessary to evaluate laboratory findings in this Phase 4 study. Full laboratory monitoring was undertaken in the adult and pediatric treatment trials and the adult and adolescent prophylaxis trials. No specific laboratory abnormalities were associated with the use of Tamiflu in those studies. The dose used for prophylaxis is half the daily treatment dose, so it was considered unlikely that significant laboratory abnormalities would be identified in this study.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In this study, temperature (fever) was recorded twice daily as part of the subject diary cards and also was documented at each clinic visit or home visit. Other vital signs were not recorded during the study.

7.1.9 Electrocardiograms (ECGs)

ECGs were not monitored in this Phase 4 study. Previous clinical trials identified no signal of potential cardiac rhythm disturbances.

7.1.12 Special Safety Studies

No special safety studies were requested or submitted with this supplement.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Tamiflu is not known to have abuse potential or to be associated with withdrawal phenomena.

7.1.14 Human Reproduction and Pregnancy Data

Tamiflu is considered Pregnancy Category C and current labeling suggests that it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There is no post-marketing data available in pregnant women.

7.1.15 Assessment of Effect on Growth

Tamiflu has been administered in pediatric patients for only short courses (5 days for treatment or 10 days for prophylaxis) and consequently effects on growth are considered unlikely. No formal assessment of growth has been conducted.

7.1.16 Overdose Experience

To date, there is no experience with overdose of Tamiflu. Single doses of up to 1000 mg have been associated with nausea and/or vomiting, as noted in the label.

7.1.17 Postmarketing Experience

The sponsor was asked to provide a safety update compiled from their global post-marketing safety database. This summary is described in more detail in Section 7.2.9.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The study submitted for review in this supplement was an open-label, randomized, Phase 4 study of the use of Tamiflu for prophylaxis against household transmission of influenza in households where the index case was also treated with Tamiflu. A total of 1110 subjects (298 index cases and 812 household contacts) were randomized to participate. Contacts were randomized as household units to receive Tamiflu QD Prophylaxis or No Prophylaxis. The Tamiflu development program included multiple other treatment studies conducted in adults, adolescents, and pediatric patients $\geq$ 1year of age and other prophylaxis studies conducted in adults and adolescents $\geq$ 13 years of age.

7.2.1.2 Demographics

In Study WV16193, a total of 1110 patients were randomized and 1104 subjects were included in the safety analysis. Two index cases and 4 contacts failed to receive study drug and were not

included in the analyses. The demographic characteristics of the index cases and contacts are shown in separate tables according to the treatment group to which the contacts were randomized. The households, randomized as units, appeared to be balanced in terms of the characteristics of their index cases (see Table 7.2.1.2A). The groups of contacts were also similar in demographic characteristics (see Table 7.2.1.2B). There were more female subjects enrolled as both index cases and contacts. Index cases tended to be younger than contacts, in keeping with the known pattern that influenza is often brought into a household via infected children. About 45% of households in both treatment groups had an index case ≤ 12 years of age. Although children < 1 year of age were not enrolled in the study, 13 households included children < 1 year of age (7 Prophylaxis group households and 6 No Treatment group households).

Table 7.2.1.2A: Demographic Characteristics of Index Cases According to Household Randomization

Demographic Characteristic	Prophylaxis (N=150)	No Prophylaxis (N=148*)
Age in years – mean (range)	20.2 (1-60)	19.7 (2-66)
median	14.0	14.0
Age ≤ 12 years	69 (46%)	65 (44%)
Sex – Male	58 (39%)	76 (51%)
Female	92 (61%)	72 (49%)
Race/Ethnicity		
White	116 (77%)	115 (78%)
Black	9 (6%)	11 (7%)
Asian	6 (4%)	9 (6%)
American Indian	1 (<1%)	0
Mixed/Other	3 (2%)	3 (2%)
Hispanic	15 (10%)	10 (7%)
Number vaccinated	10 (7%)	3 (2%)
Number with confirmed influenza**	90 (60%)	94 (64%)

*Two index cases with households randomized to No Treatment group did not receive index case treatment and are included in demographic table but not in the safety analysis tables.
**Two index cases without information regarding infection status.

Table 7.2.1.2B: Demographic Characteristics of Contacts According to Household Randomization

Demographic Characteristic	Prophylaxis (N=410*)	No Prophylaxis (N=402)
Age in years – mean (range)	27.4 (1-80)	26.4 (1-83)
median	23.5	25.0
Age ≤ 12 years	107 (26%)	115 (29%)
Sex – Male	183 (45%)	183 (46%)
Female	227 (55%)	219 (54%)
Race/Ethnicity		
White	313 (76%)	317 (79%)
Black	32 (8%)	27 (7%)
Asian	20 (5%)	28 (7%)
American Indian	0	0
Mixed/Other	8 (2%)	8 (2%)
Hispanic	37 (9%)	22 (5%)
Number vaccinated	31 (8%)	29 (7%)

*Four contacts randomized to the Prophylaxis group did not receive Tamiflu prophylaxis and are included in the demographic table but not in the safety analysis tables.

Study subjects were enrolled from 48 centers in Canada (137 subjects), Estonia (307), Finland (31), Germany (68), Sweden (29), the United Kingdom (39), and the United States (499).

7.2.1.3 Extent of exposure (dose/duration)

In Study WV16193, Tamiflu was evaluated as prophylaxis in the setting of potential household transmission in which an index case ≥ 1 year old was identified and treated with Tamiflu. Each household was randomized to receive either Tamiflu prophylaxis (half the usual daily treatment dose given QD) or treatment if household contacts developed symptomatic influenza-like illness. All household contacts who became ill were offered treatment regardless of assigned group. Consequently, some patients received no Tamiflu while others received Tamiflu QD (prophylaxis), BID (treatment of index case or ill contact), or both (failed prophylaxis followed by treatment of clinical illness).

In this study, 277 households were randomized to receive either prophylaxis for 10 days (138 households, 560 index cases and contacts) or treatment if needed (139 households, 550 index cases and contacts). A total of 1110 patients enrolled in Study WV16193, 298 as index cases and 812 as contacts. A total of 21 households had more than one index case. Two index cases did not receive treatment, 4 contacts assigned to the Prophylaxis group did not receive Tamiflu, and 8 contacts assigned to the Treatment group received QD prophylaxis with Tamiflu. Of the patients enrolled, 345 received no Tamiflu, 399 received Tamiflu QD prophylaxis, 347 received Tamiflu BID as treatment, and 17 received both some QD prophylaxis and BID treatment.

As noted in Section 6.1.3, the doses of Tamiflu used in this study for both treatment of index cases and prophylaxis were based on age rather than the weight-based doses recommended in the U.S. label. The study was initiated prior to the approval of Tamiflu in pediatric patients in the U.S. The applicant evaluated the number of pediatric patients who received more or less than the labeled dose. Among pediatric index cases who had weight data available, 35 received less than the approved dose for weight, 78 received the approved dose for weight, and 18 received greater than the approved dose for weight. Among pediatric contact cases, 30 received less than the approved dose for weight, 99 received the approved dose for weight, and 12 received greater than the approved dose for weight. According to the applicant, the safety profile in pediatric patients who received greater than the U.S. approved dose was similar to other pediatric patients.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The sponsor submitted a journal article describing an open-label, uncontrolled study of Tamiflu used for seasonal prophylaxis of influenza in a population of pediatric oncology patients reported from a hospital in Hong Kong during the 2001 flu season. According to the article, the study was supported by Roche Hong Kong Ltd who provided study drug and funding for a research assistant. (b) (4)

According to the report by Chik, et al (Hong Kong Med J, 2004; 10:103-6), 32 children between the ages of 6 and 23 years of age (median age 14 years) received Tamiflu administered once daily for 8 weeks during influenza season. Eight patients were < 10 years of age and another 11 were 10 to 14 years of age. All patients in the study received Tamiflu 75 mg once daily. The authors note that all patients had satisfactory adherence to their prophylaxis according to medication diaries. Eight patients were noted to have symptoms of influenza during the study period. None of the children in the study were reported to have laboratory-confirmed influenza but apparently only 5 patients with symptoms suggestive of influenza had rapid antigen testing performed. Some patients with symptoms of cough, runny nose, or upper respiratory tract infection did not have virologic testing for influenza. Patients had influenza serology performed but these results are not included in the paper and it is not clear that patients receiving chemotherapy or post-bone marrow transplantation would mount effective immune responses to influenza. The authors state that 5/32 (16%) of study subjects developed gastrointestinal side effects of Tamiflu and 2 subjects withdrew because of vomiting and epigastric discomfort. A total of 6 patients (19%) withdrew from the study prematurely. The authors concluded that Tamiflu given once daily for seasonal prophylaxis of influenza is safe and likely to be effective but suggested that a larger, randomized, efficacy trial should be conducted.

The major limitations of this report include its small size (particularly the small number of patients 1 to 12 years of age), lack of adequate virologic monitoring for influenza, and the lack of a control group in this more complex patient population. (b) (4)

7.2.2.2 Postmarketing experience

The sponsor was asked to provide a safety update compiled from their global post-marketing safety database. This summary is described in more detail in Section 7.2.9.

7.2.2.3 Literature

A review of the literature related to influenza in children and the safety of Tamiflu in children was conducted as part of the BPCA safety review for Tamiflu. The literature review focused primarily on neurologic and dermatologic or hypersensitivity complications of Tamiflu. No significant safety findings related to the use of Tamiflu in pediatric patients were identified in the literature.

7.2.3 Adequacy of Overall Clinical Experience

The study included in this supplement was submitted with the intent of extending the prophylaxis indication for Tamiflu to pediatric patients 1 to 12 years of age. Tamiflu is already indicated for prophylaxis of influenza in patients 13 years or older and for the treatment of uncomplicated influenza in patients $\geq$ 1 year of age. In a previously-reviewed household prophylaxis study, the duration of the prophylaxis regimen was 7 days and index cases were not treated with Tamiflu. In this study, prophylaxis was provided for 10 days along with treatment of the index case allowing for a conclusion that Tamiflu prophylaxis added to the effect that might be observed with only treatment of ill index cases in a household.

Study WV16193 was designed around a primary endpoint of the proportion of households in which at least one contact developed laboratory-confirmed clinical influenza within 10 days of the start of treatment for the index case. The study was not originally designed to evaluate the efficacy of prophylaxis specifically in children 1 to 12 years of age. However, in light of the amount of pediatric safety and efficacy data available from the treatment trials and the similarity of treatment responses between adults and children, the number of index cases (134/45%) and contacts (222/27%) in this age group was considered adequate to conclude safety and efficacy of the household prophylaxis regimen.

7.2.5 Adequacy of Routine Clinical Testing

The monitoring of clinical adverse events but not laboratory safety parameters in this study was considered reasonable in light of the amount of safety data available from previously-reviewed treatment and prophylaxis trials. The efforts to elicit reporting of adverse events in Study WV16193 were considered adequate.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the quality and completeness of the data available for review was acceptable. The proportion of subjects who had missing data was relatively small as assessed by a survey of subjects with missing diary cards. The Statistical Reviewer identified that about 60% of diary cards were completed as scheduled within 12 hours of the previous card and > 95% were completed within 18 hours of the previous card. Only a small number of subjects (3%) discontinued study prematurely.

7.2.9 Additional Submissions, Including Safety Update

Since the study submitted for this efficacy supplement was conducted some years ago, there was no safety update for any ongoing clinical trials. The sponsor was asked to provide a cumulative update of significant hepatic, renal, dermatologic, and neurologic adverse events from their post-marketing safety database. This was submitted as an amendment to the supplement and was reviewed by the Medical Officer.

The applicant evaluated their global safety database for all serious hepatic, renal, neurologic, and dermatologic events reported from all clinical trials of Tamiflu and the post-marketing spontaneous reports from all countries where Tamiflu is commercially available. In addition, they provided a table of all SAEs reported associated with off-label use of Tamiflu in children < 1 year of age. The cases were evaluated according to temporal relationship to Tamiflu use and confounding factors such as other medications and conditions. Analysis included evaluation of gender, While many of these AE reports overlap with those in the FDA AERS database, these 2 systems do not capture the same reports and should not be expected to yield identical results.

The applicant reported 121 medically significant serious dermatologic events from 106 cases in their database. The most frequently reported serious dermatologic events included rash (17) and urticaria (12). Although most of the events occurred in the 13 to 65 age group, there did not appear to be an age or gender association among these events. Most of the events occurred within 2 days of beginning Tamiflu and were reported to be improved or resolved. Ten were listed as persisting and one event was reported as worsening. Ninety-five of the 121 events (79%) were considered by the reporters to be possibly related to Tamiflu.

A total of 127 serious neurologic events from 103 cases were identified in the applicant's safety database. These events were reported occurring predominantly within the first 2 to 4 days after the use of Tamiflu. The most frequently reported serious neurologic events included convulsions (21) and depressed level of consciousness or loss of consciousness (9 and 8, respectively).

While the majority of these events were reported as improved or resolved, 4 of these events resulted in death, 4 resulted in sequelae, and 5 were listed as persisting. Seventy-two of the 127 events (57%) were considered possibly drug-related by the reporter.

The applicant identified 135 medically significant hepatic events from 110 cases, including 7 cases of "hepatic failure" and 2 cases of "fulminant hepatitis." These events were more evenly distributed over the first 2 weeks after use of Tamiflu. The most frequently reported serious hepatic events was "hepatic function abnormal" (39). Most of these events were reported to be improved or resolved but 6 resulted in death and 18 were listed as persisting. According to the applicant, review of the fatal cases identified pre-existing medical conditions or confounding concomitant medications in all cases. Eighty-six of the 135 events (64%) were considered possibly drug-related by the reporters.

Forty medically significant renal events from 38 cases were reported from the applicant's safety database. Most of these events occurred within 2 days of using Tamiflu. The most frequently reported events included renal failure (13) and acute renal failure (13). Although most of the events were reported to be improved or resolved, 3 events resulted in death and 6 events were reported to be persisting. Twenty of the 40 events (50%) were considered to be possibly related to Tamiflu by the reporters.

The table summarizing AE reports in patients < 1 year of age included 9 events from 7 cases, all reported from Japan. These cases included events of convulsions (4) and erythema multiforme, respiratory failure, encephalitis, large fontanelle, and vomiting (1 each). One event resulted in death, 2 resulted in sequelae, and the other 6 resolved. Eight of the 9 (89%) events were considered related to Tamiflu use.

The applicant concluded that analysis of these categories of events did not reveal any new information regarding the safety profile of Tamiflu and failed to suggest a causal relationship to Tamiflu. They note that in each category of events, the majority of reports were submitted from Japan. In their labeling revisions for this supplement, the applicant proposed to include some additional dermatologic events in the current Tamiflu label listing of adverse events "Observed During Clinical Practice for Treatment."

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety profile of Tamiflu has been evaluated in treatment studies conducted in all age groups $\geq$ 1 year of age and in prophylaxis studies conducted in subjects $\geq$ 13 years of age. In general, the drug has been found to be safe and well-tolerated when given either twice daily for 5 days or once daily for up to 42 days. Study WV16193 provides comparative data for both adult and pediatric patients receiving 2 different regimens of Tamiflu or no treatment. Neither subjects nor investigators were blinded to the subject's treatment assignment and safety data may have been somewhat biased by a knowledge of the subject's treatment. However, the results for this study

were in agreement with earlier studies that were randomized and blinded and it is unlikely that the limitations of this study significantly affected the safety conclusions.

No new safety findings emerged during the review of Study WV16193. The most commonly reported AEs that appear to be related to Tamiflu and dose-dependent include gastrointestinal events such as vomiting. In the full study population, vomiting occurred in about 10% of study subjects receiving Tamiflu BID, 5% of subjects receiving Tamiflu QD, and <1% of those receiving no Tamiflu. Among the subgroup of children 1 to 12 years of age, vomiting occurred in 20% of those receiving Tamiflu BID, 10% of subjects receiving Tamiflu QD, and 2% of those receiving no Tamiflu. No deaths were reported during the study period. A small number of study subjects (5) developed serious AEs requiring hospitalization. None of these events were considered related to study drug. Similarly, a small number of study subjects (5) discontinued their Tamiflu treatment or prophylaxis prematurely because of AEs. Three of the 5 subjects who prematurely discontinued study drug did so because of nausea and/or vomiting.

A post-marketing safety update conducted using the applicant's global post-marketing safety database and the FDA AERS database provided additional safety data during this supplement review. The DDRE review of these post-marketing safety data suggests that additional precautionary language regarding serious skin/hypersensitivity reactions may be warranted. AERS reports of serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, and erythema multiforme were identified and review of these cases suggest a possible association with the use of Tamiflu. These events occur too infrequently to be adequately evaluated using the available clinical trials data but may represent drug-related toxicity.

In conclusion, the use of Tamiflu once daily for 10 days as prophylaxis in the setting of household exposure to influenza was found to be safe and well-tolerated. The safety profile was acceptable in all age groups evaluated although it appears that pediatric patients may have somewhat higher rates of gastrointestinal adverse events than adults. Serious skin/hypersensitivity reactions should be updated in the label safety information.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Since this submission contained data from a single study, no pooling of data across studies was performed.

7.4.2 Explorations for Predictive Factors

A formal exploration of predictive factors for drug-related AEs was not performed. However, this study provides additional data suggesting that the gastrointestinal AEs associated with Tamiflu, especially vomiting, are dose-related. In Study WV16193 it is clear that subjects receiving Tamiflu treatment BID had the highest rates of vomiting, and those receiving Tamiflu QD prophylaxis had higher rates of vomiting than those receiving No Prophylaxis. As in previously-reviewed studies of Tamiflu treatment, it appears that children may have higher rates of vomiting than adults.

7.4.3 Causality Determination

Review of the data from this and other clinical trials suggest that Tamiflu may cause nausea, vomiting, and/or other gastrointestinal adverse events in patients receiving the drug for either treatment or prophylaxis. Gastrointestinal events have been reported in patients with influenza in the absence of treatment, especially in pediatric patients, but the clinical data suggest a dose-dependent effect. Although they were not identified in the clinical trials, Tamiflu may also contribute to uncommon but serious skin/hypersensitivity reactions as reported in post-marketing databases.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The doses used for prophylaxis and treatment in patients 1 to 12 years of age in Study WV16193 were based on age. (b) (4)

The approved dose for prophylaxis of influenza in patients > 13 years of age is Tamiflu 75 mg given once daily, half the approved treatment dose. In all previous prophylaxis studies, this dosing regimen was shown to be effective. The selection of dosing for pediatric patients was

also half the treatment dose, based on the proposal for dosing at the time of study initiation. The DAVP Review Team continues to believe that weight-based dosing is appropriate for the U.S. pediatric population and does not feel that an extrapolation of these study results to a weight-based dose recommendation is problematic. The prophylaxis doses recommended for patients 1 to 12 years of age are:

≤ 15 kg (≤ 33 lb)	30 mg QD x 10 days
> 15 kg – 23 kg (> 33 lb – 51 lb)	45 mg QD x 10 days
> 23 kg – 40 kg (> 51 lb – 88 lb)	60 mg QD x 10 days
> 40 kg (> 88 lb)	75 mg QD x 10 days

Previously, Tamiflu prophylaxis was recommended for a period of 7 days following close contact with an infected person (post-exposure prophylaxis). The current study evaluated a post-exposure prophylaxis regimen of 10 days. Efficacy of the 7-day regimen has not been evaluated in pediatric patients but both regimens have acceptable safety profiles. To provide consistent recommendations for post-exposure prophylaxis, the recommendations for dosing adults and adolescents will be revised to reflect the 10-day regimen.

(b) (4)

the DAVP Review Team will request that the applicant collect safety data in pediatric patients given up to 6 weeks of Tamiflu in the setting of community outbreak or seasonal prophylaxis.

8.8 Other Relevant Materials

A review of the AERS database of events reported in association with Tamiflu use was conducted by Evelyne Edwards, Post-Marketing Safety Evaluator, DDRE. She evaluated the cumulative reports of serious hepatic, renal, neuropsychiatric, and serious skin and hypersensitivity reactions reported in association with Tamiflu use in all age groups. A copy of her completed consult is included in the supplemental NDA approval package. Her conclusions will be briefly summarized below. As noted in Section 7.2.9, although many of the AERS reports overlap with those in the applicant's safety database, these 2 systems do not capture the same reports and should not be expected to yield identical results.

A search of the AERS database identified 21 cases of serious hepatic toxicity, including 14 cases of hepatic failure, and 43 cases of serious renal toxicity, including 18 cases of renal failure. These cases were confounded by the use of other medications and the presence of other medical conditions. No cases appeared to have a clear causal relationship with Tamiflu. No changes in the safety language regarding these events were proposed as a result of the review.

The AERS search identified 126 reports of neuropsychiatric AEs, including 3 deaths, in all age groups. Most of these cases were reported in pediatric patients. The etiology of these events and

a possible relationship to Tamiflu use was frequently difficult to interpret because many of the reports lacked sufficient detail to assess causality. Also, many of the reports were from foreign sources (especially Japan) where medical care may be different than in the U.S., where follow-up of AEs is difficult, and where we are dependent on translated reports. The neuropsychiatric events described such as delirium, convulsions, and altered consciousness were also similar to events that have been described in association with influenza. Some of the neuropsychiatric events described as "abnormal behavior" were unusual and not completely explained as a manifestation of influenza. Although no change in labeling regarding neuropsychiatric events is currently recommended, DDRE and the DAVP Review Team will continue to monitor closely for this type of event as Tamiflu use increases in the U.S. population.

A total of 43 cases of serious skin/hypersensitivity reactions were identified in the AERS search. As with the neuropsychiatric cases, a majority of the reports were from Japan but there were also reports from the U.S., Europe, and Australia. These reports included 24 cases of Stevens-Johnson syndrome, 14 cases of erythema multiforme, 4 cases of toxic epidermal necrolysis, and one case of pemphigus. Unlike the other categories of events, a majority of the serious skin reactions were considered likely to be associated with Tamiflu use. This association was based on the following criteria: a temporal relationship between the event and the use of Tamiflu, lack of other confounding medications, lack of a known significant association between serious skin reactions and influenza, and a known association between these types of events and drugs in general. As detailed in Section 9.4, these findings prompted DDRE and the DAVP Review Team to recommend new safety language regarding serious skin/hypersensitivity reactions in the Tamiflu label.

9 OVERALL ASSESSMENT

9.1 Conclusions

Based on the results of Study WV16193, the FDA Clinical and Statistical Reviewers concluded that Tamiflu administered once daily as prophylaxis was effective in limiting household transmission among exposed contacts when they were provided prophylaxis for 10 days beginning within 48 hours of identification and start of treatment of the index case. Data collection, selection of endpoints, and efficacy and safety analyses were adequate and appropriate to determine that Tamiflu was beneficial in the study setting. The design of this study allowed confirmation that there was additional benefit in the use of prophylaxis above that of only treating the ill index case in the household. The benefit of prophylaxis was shown in both adults and adolescents $\geq$ 13 years of age, the group for whom Tamiflu is currently indicated for prophylaxis, and in household contacts 1 to 12 years of age. Secondary efficacy analysis documented that among those contacts who developed clinical influenza, those who received Tamiflu prophylaxis were ill for a shorter period of time than those who did not receive prophylaxis. Additionally, there was no evidence that Tamiflu-resistant influenza virus was generated or transmitted within households or emerged among those contacts who developed influenza in spite of receiving prophylaxis.

Independent FDA statistical analysis of the study data confirmed the applicant's findings and conclusions and differences in efficacy analysis results were minimal and clinically insignificant. According to the FDA analysis, the risk of at least one new contact (not shedding influenza virus at baseline) per household developing laboratory-confirmed, clinical influenza in the setting of confirmed infection in the index case was reduced from 22% in households not receiving prophylaxis to 5% in those receiving Tamiflu once daily for 10 days (P=0.0004). Similarly, the risk of confirmed, clinical influenza among individual contacts not already shedding influenza virus at baseline was reduced from 11% in those contacts not receiving prophylaxis to 2% in those receiving Tamiflu (P<0.0001). In sensitivity analyses, the benefit of prophylaxis was confirmed regardless of the infection status of the index case or the baseline infection status of the contacts.

These efficacy data are consistent with other studies of Tamiflu as prophylaxis against influenza. Earlier studies conducted in adults and adolescents $\geq$ 13 years of age have shown that Tamiflu is effective in decreasing transmission of influenza in household and institutional settings and can be administered for up to 42 days for seasonal prophylaxis. The current submission provides the only reviewable data in patients 1 to 12 years of age and the benefit of prophylaxis in the age subgroup targeted was documented. In the subgroup of 1 to 12 year olds, the proportion of contacts not shedding influenza virus at baseline who developed confirmed, clinical influenza decreased from 17% in those not receiving prophylaxis to 3% in those receiving prophylaxis (P=0.0006). This analysis will be displayed in the revised Tamiflu label as it provides the broadest, most appropriate pediatric population showing significant benefit from prophylaxis.

The safety profile of Tamiflu has been previously evaluated in treatment studies conducted in all age groups $\geq$ 1 year of age and in prophylaxis studies conducted in subjects $\geq$ 13 years of age. In those studies, the drug has been found to be safe and well-tolerated when given either twice daily for 5 days or once daily for up to 42 days.

No new safety findings emerged during the review of Study WV16193. The most commonly reported AEs that appear to be related to Tamiflu and dose-dependent include gastrointestinal events such as vomiting. In the full study population, vomiting occurred in about 10% of study subjects receiving Tamiflu BID, 5% of subjects receiving Tamiflu QD, and <1% of those receiving no Tamiflu. Among the subgroup of children 1 to 12 years of age, vomiting occurred in 20% of those receiving Tamiflu BID, 10% of subjects receiving Tamiflu QD, and 2% of those receiving no Tamiflu. No deaths were reported during the study period. A small number of study subjects (5) developed serious AEs requiring hospitalization. None of these events were considered related to study drug. Similarly, a small number of study subjects (5) discontinued their Tamiflu treatment or prophylaxis prematurely because of AEs. Three of the 5 subjects who prematurely discontinued study drug did so because of nausea and/or vomiting.

A post-marketing safety update conducted using the applicant's global post-marketing safety database and the FDA AERS database provided additional safety data during this supplement review. Review of these post-marketing safety data suggests that additional precautionary language regarding serious skin/hypersensitivity reactions may be warranted. AERS reports of serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria,

and erythema multiforme were identified and review of these cases suggests a possible association with the use of Tamiflu. These events occur too infrequently to be adequately evaluated using the available clinical trials data but may represent drug-related toxicity.

9.2 Recommendation on Regulatory Action

After completing an independent Clinical Review of this supplement, this Medical Officer recommends that the indication for Tamiflu in post-exposure prophylaxis against influenza be extended to include pediatric patients 1 to 12 years of age. This recommendation is based on review of the safety and efficacy data for Study WV16193, a study evaluating the effectiveness of Tamiflu given for 10 days in preventing household transmission of influenza. The subgroup of household contacts 1 to 12 years of age who received Tamiflu prophylaxis for 10 days developed confirmed, clinical influenza significantly less often than those who did not receive prophylaxis. No serious or significant toxicity was identified that would outweigh the benefits of prophylaxis although a higher proportion of pediatric contacts receiving prophylaxis reported vomiting than those not receiving prophylaxis.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Tamiflu has been approved for the treatment of influenza in patients > 1 year of age and for prophylaxis in patients > 13 years of age. To date, no special risk management strategies have been proposed by the applicant or requested by the FDA. The applicant continues to provide safety updates in the form of Annual Reports. The applicant also collects post-marketing reports of AEs through their global safety network which are then submitted to the FDA AERS database. During active influenza season when drug use is highest, AERS cases related to all influenza

antiviral drugs are monitored in an on-going basis by the ODS Safety Reviewer and the Clinical Reviewer. These data are shared with staff at the Centers for Disease Control and Prevention and correlated with their active influenza surveillance data as part of the safety monitoring for this therapeutic class.

9.3.2 Required Phase 4 Commitments

(b) (4)

The DAVP Review Team has requested the following post-marketing commitment:

> Collect and submit safety data in a population of 40-50 pediatric patients 1 to 12 years of age using the approved prophylaxis dosing recommendations for a period of up to 6 weeks in the setting of seasonal influenza prophylaxis. Evaluation of "influenza high risk" patient groups is suggested.
> Submit protocol by December 1, 2006
> Submit final study report by July 1, 2008

9.3.3 Other Phase 4 Requests

There are no additional recommended or optional post-marketing commitments related to this supplement.

9.4 Labeling Review

The major label revisions proposed with this efficacy supplement involve additions of a description of Study WV16193, a change in the age range for prophylaxis, revisions to the pediatric and adult safety data, inclusion of serious skin reactions in the Precautions section, and addition of the recommended doses for prophylaxis in the pediatric population. In the current Tamiflu label, only a single indication for prophylaxis of influenza is identified in the Indications section, not separate indications for post-exposure prophylaxis and seasonal prophylaxis. This issue is addressed in the Dosage and Administration section of the label where a distinction is made between prophylaxis following close contact with an infected individual and prophylaxis during a community outbreak of influenza. The revised label now recommends prophylaxis for 10 days for all age groups following close contact with an infected person in order to maintain consistency. (b) (4)

The proposed package insert (label) has been reviewed by all disciplines involved in the NDA supplement review. The major recommendations for revisions to the clinical sections of the proposed label are itemized below. These changes have been discussed with and agreed upon by the applicant.

1. In the display of efficacy results for patients 1 to 12 years of age, consider providing the analysis of contacts not shedding influenza at baseline who developed confirmed, clinical influenza regardless of the infection status of the index case. Use of this population includes those contacts who may have derived short-term prophylaxis benefit against community-acquired influenza. This represents a broader population than the proposed ITTIINAB population.

2. (b) (4)

3. Please include patients ≥ 13 years of age enrolled in study WV16193 in Table 3, "Most Frequent Adverse Events…In Patients 13 Years of Age and Older." The randomized contacts in this study (prophylaxis vs. no prophylaxis) can be combined with those from the previously reviewed prophylaxis studies (prophylaxis vs. placebo).

4. Please move the paragraph "Prophylaxis Studies in Adult Patients" ahead of Table 3 in the label.

5. In Table 4, the footnotes describing Study WV16193 are not clear. Please describe the study more fully: for example, a randomized, open-label study of household transmission in which some pediatric patients received prophylaxis and others received treatment for influenza. Also provide the dosing actually used in the study. Pediatric dosing in the U.S. is weight-based, not age-based, so reference to the Dosage and Administration section will not provide the dosing used in the study. Also, there may need to be slightly different headings for the Table so that it is clear that the last 2 columns represent different groups in the same study. After re-evaluating the text and tables in the proposed label, we believe that Table 4 will provide more useful information for practitioners if the column (b) (4) is deleted and replaced with a column showing the AEs in those patients randomized to No Prophylaxis who never received Tamiflu treatment. This would make the table more analogous to Table 3 and would provide a useful comparison between uninfected pediatric patients receiving and not receiving Tamiflu. See example:

Adverse Event	Treatment Trials		Household Prophylaxis Trial	
	Placebo (N=517)	Oseltamivir 2 mg/kg BID (N=515)	No Treatment (N=92)	Prophylaxis with Oseltamivir QD (N=99)
Vomiting				
Diarrhea				

6. Please move the section Prophylaxis Study in Pediatric Patients to a position before Table 4. Please delete the word (b) (4) from the heading for this section. (b) (4)

[redacted]. Add to the last sentence, "…consistent with those previously observed in pediatric treatment studies (see Table 4)."

7. In reviewing the safety data submitted and preparing for the recent Pediatric Advisory Committee meeting, we have consulted with the Office of Drug Safety, Division of Drug Risk Evaluation. They have completed an independent review of post-marketing safety reports submitted to the FDA AERS database. It is our conclusion that serious skin/hypersensitivity reactions have been associated with Tamiflu use, without other likely explanations in some cases. We believe that new language regarding these events should be included in the PRECAUTIONS section as follows:

> Serious skin/Hypersensitivity Reactions: Anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported in post-marketing experience with Tamiflu. Tamiflu should be stopped and appropriate treatment instituted if an allergic-like reaction occurs or is suspected.

8. In the section, "Observed During Clinical Practice for Treatment," please delete the phrase [redacted] in the heading since these reactions are likely not to be specific to treatment. Under the listing "Dermatologic," please delete the phrase [redacted] and include the listed conditions and a reference to "(see PRECAUTIONS)".

9. In the Dosage and Administration section, the pediatric prophylaxis dose should be described as follows (lines 489-90), "Prophylaxis is recommended for 10 days in pediatric patients following close contact with an infected individual. Prophylaxis in patients 1 to 12 years of age has not been evaluated for longer than 10 days duration. Therapy should begin within 2 days of exposure."

10. In the Precautions section, please re-insert the statement, "Safety and efficacy of repeated treatment or prophylaxis courses have not been studied."

Comments regarding the Patient Package Insert:

10. In the section "How Should I take Tamiflu," please include a statement that Tamiflu has not been evaluated in pediatric patients for prophylaxis longer than 10 days and/or has not been studied pediatric patients for prevention during community outbreaks of flu.

11. Please include a section in the PPI that describes the occurrence of serious skin and hypersensitivity reactions. Patients should be instructed to stop taking Tamiflu and contact their health care provider if they develop a severe rash.

9.5 Comments to Applicant

At this time, all comments pertinent to the review of this efficacy supplement and revisions to the Tamiflu label have been forwarded to the applicant and are described in Section 9.4. No additional comments need to be conveyed to the applicant.

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/s/

Linda Lewis
12/20/2005 04:17:56 PM
MEDICAL OFFICER
Approval with labeling changes recommended.

Kathrine Laessig
12/20/2005 04:25:45 PM
MEDICAL OFFICER

Debra Birnkrant
12/21/2005 08:58:06 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21246/S-017

CHEMISTRY REVIEW(S)

Efficacy Supplement
Evaluation of Chemistry, Manufacturing and Controls

NDA 21-246 / SE5-017

Letter Date: 15-Apr-2005
CDER Stamp Date: 18-Apr-2005

Planned Action Date: 21-Dec-2005

1) Check all categories of CMC-related changes that are proposed in this efficacy supplement:

New Environmental Assessment data, or a change in exemption status, related to increased use or expanded patient population (e.g., SE6: Rx-to-OTC switch)	☐
Manipulation of drug product, or active control drug, or placebo, either for PK studies or for marketing (e.g., grinding tablets to make unmarked capsules; change in tablet scoring; repackaging of clinical supplies except for solid oral products)	☐
Changes in "Description," or "How Supplied" sections of Package Insert that are relevant to CMC (e.g., change in container/closure; change in amount of fill)	☐
Changes in the "Dosage and Administration" section of Package Insert that involve preparation of the product or delivery to the patient (e.g., preparation or storage of a reconstituted liquid, dilution prior to injection, scoring, syringe calibration, extemporaneous compounding)	☐
Changes in Container or Carton Text or Artwork	☐
Change to, or introduction of, a professional sample	☐
Changes in Patient Package Insert that are relevant to CMC	☐
Other changes needing a CMC evaluation. Specify in Section 2, below	☐

2) Evaluation of issues noted in Part 1.

This supplement provides for the extension of the prohylaxis indication for Tamiflu (oseltamivir phosphate) to patients 1-12 years of age. This minor increase in the patient population will not trigger the requirement for an Environmental Assessment. This efficacy supplement has been evaluated from the CMC perspective and there are no issues that need to be documented.

3) Recommendation from CMC perspective:

Recommended for approval from the CMC perspective.

{signed electronically in DFS}
George Lunn, Ph.D.

15-Dec-2005
Date

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/s/

George Lunn
12/16/2005 08:52:37 AM
CHEMIST

Efficacy supplement - no CMC issues

Norman Schmuff
12/16/2005 03:19:05 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

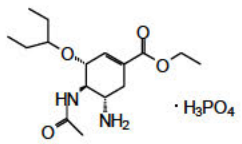
NDA 21246/S-017

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA Number:	21,087 & 21,246
Review Number:	
Sequence Number/Date/Type Of Submission:	030 & 017/Dec. 21, 2001/SEI
Information To Sponsor:	Yes ( ) No (X)
Sponsor and/or Agent:	Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, NJ 07110-1199
Manufacturer For Drug Substance:	F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124 CH-4070 Basel, Switzerland
REVIEWER NAME:	Ita Yuen
DIVISION NAME:	Division of Antiviral Drug Products
HFD #:	530
Review Completion Date:	12/20/05

Drug:

Trade name:	Tamiflu®
Generic name (list alphabetically):	Oseltamivir phosphate
Code name:	Free base: Ro 64-0796/000; GS-4104 Phosphate salt: Ro 64-0796/002; GS-4104-02
Chemical name:	(3R,4R,5S)-4-(acetylamino)-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid ethyl ester, phosphate (1:1)
CAS registry number:	204255-11-8
Mole file number:	
Molecular formula/molecular weight:	$C_{16}H_{28}N_2O_4$ (free base)/M.W. = 312.41 $C_{16}H_{28}N_2O_4$ 1:1 H_3PO_4 (phosphate salt)/ M.W. = 410.408
Structure:	

Relevant INDs/NDAs/DMFs:	IND 53,093 DMF Type I #'s (b) (4) DMF Type III #'s (b) (4) DMF Type IV #'s (b) (4)
Drug class:	Influenza viral neuraminidase inhibitor
Indication:	Treatment and prophylaxis of influenza
Clinical formulation:	The drug product is being supplied as 75-mg (75 mg free base equivalent to 98.5 mg of the

	phosphate salt) gray/light yellow hard gelatin capsules. The excipients contain [redacted] pre-gelatinized starch, [redacted] Povidone K 30, [redacted] croscarmellose sodium, [redacted] Talc, [redacted] sodium stearyl fumarate.
Route of administration:	Oral
Proposed use:	75 mg

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Tamiflu has been approved for the treatment and prophylaxis of influenza in adults. The present supplements seek to extend the prophylaxis indication to 1-12 years old children. There is no new nonclinical pharmacology/toxicology information. The nonclinical pharmacology/toxicology requirement for the approvability of this indication in children is the same as that for the adults. Therefore, the application is recommended for approval from the nonclinical pharmacology/toxicology perspective.

B. Recommendation for Nonclinical Studies

Not applicable.

C. Recommendations on Labeling

Not applicable

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

Not applicable.

B. Pharmacological Activity

Not applicable.

C. Nonclinical Safety Issues Relevant to Clinical Use

Not applicable.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

cc: list: HFD-530/NDA 21,087 & 21,246(030 & 017)
HFD-530/Division File
HFD-530/JO'Neil
HFD-530/LLewis

HFD-530/GLunn
HFD-530/NBattula
HFD-345

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/s/

Ita Yuen
12/20/2005 10:05:53 PM
PHARMACOLOGIST

James Farrelly
12/22/2005 09:43:19 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21246/S-017

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#:	21-246/S-017
DRUG NAME:	Tamiflu® (Oseltamivir)
INDICATION:	Prophylaxis of Influenza Infection
TYPE OF REVIEW:	Clinical
APPLICANT:	Hoffman-La Roche Inc.
DATES:	April 2005/December 2005
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	DB3
STATISTICAL REVIEWER:	Thomas Hammerstrom, (HFD-725)
TEAM LEADER:	Greg Soon, PhD, (HFD-725)
MEDICAL DIVISION:	DAVP
CLINICAL TEAM:	Linda Lewis, MD (HFD-530)
PROJECT MANAGER:	Jeff O'Neil (HFD-530)

STATISTICAL REVIEW AND EVALUATION

NDA#: 21-246

1. Executive Summary

The applicant submitted one randomized, controlled phase III clinical trials with tamiflu for this application: trial WV16193. The primary objective of study WV16193 was to compare the efficacy of once daily tamiflu to that of no treatment for the prophylaxis of influenza in uninfected members of households with one index influenza case. The index case was receiving tamiflu bid for treatment of his influenza.

In conjunction with a prior submission, the applicant has established that tamiflu, used in 30-75 mg qd (depending on age) for 10 days was effective as a prophylactic against influenza when prophylaxis was started promptly after the diagnosis of a family member with influenza. The risk of at least one new member of the family contacting influenza from 22% with only the index case being treated to 5% with prophylaxis. Measured on an individual basis, the risk was reduced from 11% to 2%. Even the index case were not infected, the prophylaxis was effective in reducing the risk of community acquired influenza from 5% to 2%.

This pattern was consistent across ages, with reduction in risk for the youngest subjects being from 20% to 11% for those under the age of 5 and from 19% to 7% for those under the age of 12.

There was also an apparent reduction of 3-4 days in the duration of symptoms for those subjects who did contact influenza despite prophylaxis.

The results were consistent across age group, sex, and race.

2. Introduction

2.1 Overview

The applicant submitted one randomized, controlled phase III clinical trials with tamiflu for this application: trial WV16193.

2.2 Data Sources

2.2.1 Objectives in Trials

The primary objective of study WV16193 was to compare the efficacy of once daily tamiflu to that of no treatment for the prophylaxis of influenza in uninfected members of households with one index influenza case. The index case was receiving tamiflu bid for treatment of his influenza.

The basic unit of the study was the household and the primary efficacy endpoint was the percentage of households with at least one influenza infection among the contact subjects uninfected at baseline. The study population consisted of households with 3 to 8 individuals. Of these, at least one was an index case with less 48 hours of illness characterized by rapid onset of fever (>=37.8° C) plus cough or coryza, at least two were eligible contacts (not ill at baseline and older than one year), and at most one was an ineligible contact (younger than one year).

2.2.2 Summary of Study Design

The trial was an open-label, randomized, two-arm, parallel, untreated controlled, multi-center trial, conducted at 101 centers, 62 in North America and 39 in Europe. Households were randomly assigned in a 1:1 ratio to control and prophylaxis arms. The randomization was stratified by number of eligible contacts and number of index cases.

In both arms, the index case(s) received tamiflu treatment with dose adjusted for age as follows:

30 mg bid for children 1-2 years old

45 mg bid for children 3-5 years old
60 mg bid for children 6-12 years old
75 mg bid for subjects > 12 years old.
The treatment lasted 5 days as indicated in the tamiflu label.

In the control arm, the contacts received no treatment unless and until they developed symptoms of influenza. In the prophylaxis arm, eligible contacts received tamiflu with dose adjusted for age as follows:
30 mg qd for children 1-2 years old
45 mg qd for children 3-5 years old
60 mg qd for children 6-12 years old
75 mg qd for subjects > 12 years old.
The prophylaxis lasted 10 days.

In both arms, contacts who developed symptoms of influenza, as diagnosed by a health care professional, could receive a five day course of bid tamiflu to treat the influenza.

2.2.3 Patient Accounting and Baseline Characteristics

277 households, represented by 298 index cases, were randomized in trial WV16193. Table 2.2.3 A summarizes the primary reasons for discontinuation from the study and from treatment. This table was produced from the applicant's dataset EXIT and is slightly discrepant from their figure 1 in section 3.1.1 of their NDA report.

TABLE 2.2.3 A
PATIENT STATUS, TRIAL WV16193

	Prophylaxis	Control
Index Cases	154	144
Completed	151	136
Completed/AE	0	3
Withdrew AE	0	1
Withdrew	3	4
Contact Cases	420	392
Completed	135	379
Completed/AE	3	1
Withdrew AE	0	0
Withdrew	10	12

The subjects were enrolled at 48 centers in Canada, Estonia, Finland, Germany, Sweden, Britain, and the US (17 centers).

Baseline demographic traits and other characteristics of the households and of the individual subjects are summarized below. Table 2.2.3 B gives the number of households by number of index cases and by number of contacts, together with the number of individual contacts in each size household.

TABLE 2.2.3 B
NUMBER OF CASES AND CONTACTS PER HOUSEHOLD

	Prophylaxis		Control	
Index case	HH	Pats	HH	Pats
1	128		128	
2	13		8	
Contacts				
1	0	0	1	3
2	62	188	55	168
3	43	174	45	183
4	19	94	29	146
5	8	49	7	43
6	3	22	3	23
>=7	1	9	1	8

In trial WV16193, the study subjects were 55% female. They were 86% white, 7% black, and 7% other or mixed. (Index cases

and contacts had the same gender racial mix.) They had a mean age of 20 years for index cases and of 27 years for contacts. 43% of contacts and 61% of index cases were children. See table 2.2.3 C.

TABLE 2.2.3 C
AGE DISTRIBUTION OF INDEX CASES AND CONTACTS

Age	Index cases	Contacts
<1	4	3
1-12	130	219
13-18	47	131
>18	117	459

2.2.4 Summary of Methods of Assessment

2.2.4.1 Schedule of Measurements

Index cases recorded their influenza symptoms and their temperatures bid on diary cards for days 1-30. They also had clinic visits with throat and nasal swabs at baseline (day 1 pre-dose) and day 6, and with blood for influenza antibodies at baseline and day 30.

Eligible contacts also recorded symptoms and temperatures bid on diary cards from baseline to day 30. They had clinic visits with throat and nasal swabs on days 1 and 10 of the study. If they developed influenza symptoms, they also had clinic visits with throat and nasal swabs on days 1 and 6 of their symptoms. The earlier of these two swabs preceded their beginning their 5 day course of bid tamiflu. Finally, the contacts had blood for influenza antibodies on days 1 and 30 of the study.

2.2.4.2 Assessment of Treatment Effects

The protocol specified primary endpoint was the percentage of households with at least one confirmed influenza case among the eligible contacts. A confirmed influenza case consisted of fever plus cough or coryza plus lab confirmation. Lab confirmation was positive viral shedding within 2 days of onset of fever or >= 4-fold increase in influenza antibody titer

between baseline and day 30.

2.2.5 Summary of Statistical Analysis

The Fisher exact test was used to compare the prophylaxis and control arms with respect to percentage of households with at least one contact developing influenza. The applicant originally planned to stratify the analysis by two binary variables: presence/absence of two or more eligible contacts and presence/absence of a child under the age of one. Because there were too few cases in some of the strata, this analysis was not possible.

There is no mention of stratifying the analysis by the stratifying variables used in the randomization (number of eligible contacts and number of infected index cases).

The analyses were repeated for three nested populations: ITT (all randomized households), ITTII (those with index cases confirmed infected with influenza), and ITTIINAB (those in the ITTII population with eligible contacts with no influenza virus at baseline

2.2.6 Summary of Applicant's Results

62% (184/298) of index cases were confirmed to have influenza. Of these, 66% (121) had influenza type A and the others had influenza type B. The primary efficacy endpoint, percentage of households in which one or more contacts had influenza confirmed by both symptoms (cough or coryza plus fever >=37.8° C) and by virology is summarized in table 2.2.6 A for the ITTII population.

TABLES 2.2.6 A
CONFIRMED INFLUENZA AMONG CONTACTS

	Prophylaxis	Control
Infected Index cases	90	94
Infected HH	84	89
No Infected Contacts	75 (89%)	66 (74%)
>= 1 Infected Contact	9 (11%)	23 (26%)

Protective Efficacy = 1 - relative risk of flu =
59% with 95% confidence limits = (16%, 80%)

(Presumably 11 of the households had either two infected index cases or zero contacts.)

Table 2.2.6 B gives the same efficacy analysis for the slightly ITTIINAB population, where at least one contact per household was negative at baseline for influenza virology.

TABLES 2.2.6 B
CONFIRMED INFLUENZA AMONG NAB CONTACTS

	Prophylaxis	Control
Infected HH	84	89
No Infected Contacts	80 (95%)	69 (78%)
>= 1 Infected Contact	4 (5%)	20 (22%)

Protective Efficacy = 1 - relative risk of flu =
79% with 95% confidence limits = (41%, 92%)

(This analysis removes some infected contacts by observing that they appear to have been already infected at baseline. Thus, the estimated risk of flu goes down in both arms.)

One might also look at the incidence rate of confirmed flu among all contacts. (This was not the primary analysis because it ignores correlations among controls in the same household.) The results looking at rates this way is given in table 2.2.6 C.

TABLE 2.2.6 C
CONFIRMED INFLUENZA AMONG CONTACTS, IGNORING HH

	Prophylaxis	Control
Exposed Contacts	244	258
Uninfected Contacts	234 (96%)	225 (87%)
Infected Contacts	10 (4%)	33 (13%)

Protective Efficacy = 1 - relative risk of flu =
68% with 95% confidence limits = (35%, 84%)

All three ways of looking at the data show the same statistically significant pattern of prophylactic efficacy.

2.2.7 Summary of Applicant's Conclusions

The applicant concluded that post exposure prophylaxis with oseltamivir is more effective than mere treatment of the infected case in preventing the secondary spread of influenza infection in households. The efficacy was the same in children under 12 years of age as in older exposed subjects.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Replication of Primary Analysis

The FDA statistical reviewer was not able to reproduce the exact numbers obtained by the applicant. The results obtained by the reviewer's independent calculation of incidence and duration of flu are given in the following sections. One will notice that these results lead to the same conclusions as those obtained by the applicant. Tamiflu, taken prophylactically for 10 days at 75 mg qd (or adjusted to lower doses for children) was clinically and statistically significantly superior to placebo in reducing incidence of virally confirmed symptomatic flu.

Table 3.1.1 A presents a summary of incidence of virally confirmed symptomatic flu, first by household and then by individual contacts. The former analysis is statistically preferable because the analysis by individual ignores the potentially correlated risks of subjects whose primary exposure is the same infected index case. Six results are presented for households and six for individuals. The first three are use any contacts, whether or not they had flu antibodies at baseline. There are three possible infection sources: any, community, or index case. "Any" contains the results for all households or all contacts, regardless of the status of the index case. "Community source" contains the results only for households with non-infected index case; "index case source" contains the results for infected index case. The second group of three results contains results in which only contacts who were negative at baseline (NAB) for flu antibodies were counted. The three results are sorted the same as above with respect to status of the index case. Each line of the table gives the potential source of infection, the incidence rate for control and prophylaxed arms, the difference and 95% confidence limits on the difference (using a z approximation) and the two-sided Fisher exact p-value for the difference.

TABLE 3.1.1 A
INCIDENCE OF INFECTION

Infection Source	Mean Diff	95% Limits Lower	Upper	Control	Prophy	Fisher P-value
Households						
Any	12.4%	4.4%	20.5%	27/136=20%	10/135=7%	.0024
Community	6.5%	-2.3%	15.4%	4/47=9%	1/51=2%	.15
Index_Case	15.1%	3.9%	26.4%	23/89=26%	9/84=11%	.0084
Households, NAB						
Any	13.9%	6.8%	21.1%	24/136=18%	5/135=4%	.0001
Community	6.5%	-2.3%	15.4%	4/47=9%	1/51=2%	.15
Index_Case	17.7%	7.9%	27.5%	20/89=22%	4/84=5%	.0004
Contacts						
Any	7.5%	4.1%	10.9%	40/392=10%	11/400=3%	<.0001
Community	4.6%	0.6%	8.6%	7/134=5%	1/156=1%	.024
Index_Case	8.7%	3.9%	13.5%	33/258=13%	10/244=4%	.0004
Contacts, NAB						
Any	7.9%	4.8%	11.0%	35/380=9%	5/383=1%	<.0001
Community	4.7%	0.6%	8.7%	7/132=5%	1/155=1%	.023
Index_Case	9.5%	5.2%	13.8%	28/248=11%	4/228=2%	<.0001

One can see that in all cases, regardless of whether the unit of analysis is the household or the individual contact, regardless of whether the contact was NAB or not, regardless the source of risk was an infected index case or community exposure, prophylaxed contacts were at lower risk than control contacts. When the index case was infected, the risk was statistically significantly lower, 10-20% lower. Even when the index case was not infected, the risk of exposure from the community was estimated to be 5-7% lower, although this could have been due to chance variability, since statistical significance in this sub-population was not achieved.

One gets similar results if one looks at symptomatic flu, possibly without confirming virology, or viral shedding, possibly without symptoms. Symptomatic flu is just the result of pooling confirmed flu, which tamiflu prophylaxis reduces, with diseases merely resembling flu, on tamiflu prophylaxis has no effect. We therefore omit these results. Table 3.1.1 B shows the results for flu virology, regardless of symptoms. The results in this

table are displayed in the same format as table 3.1.1 A.

TABLE 3.1.1 B
INCIDENCE OF INFLUENZA VIROLOGY

Infection Source	Mean Diff	95% Limits Lower	Upper	Control	Prophy	P-value
Households						
Any	11.2%	-0.3%	22.7%	60/137=44%	44/135=33%	.056
Community	11.8%	-3.8%	27.4%	12/47=26%	7/51=14%	.14
Index_Case	9.3%	-5.5%	24.1%	48/90=53%	37/84=44%	.22
Households, NAB						
Any	14.2%	3.2%	25.3%	55/137=40%	35/135=26%	.012
Community	11.6%	-3.4%	26.6%	11/47=23%	6/51=12%	.13
Index_Case	14.4%	-0.1%	28.9%	44/90=49%	29/84=35%	.052
Contacts						
Any	10.6%	5.2%	15.9%	95/395=24%	54/400=14%	.0001
Community	9.1%	2.2%	15.9%	19/134=14%	8/156=5%	.0096
Index_Case	10.3%	2.9%	17.6%	76/261=29%	46/244=19%	.0064
Contacts, NAB						
Any	11.8%	6.7%	16.9%	82/382=21%	37/383=10%	<.0001
Community	8.4%	1.8%	14.9%	17/132=13%	7/155=5%	.0128
Index_Case	12.8%	5.9%	19.8%	65/250=26%	30/228=13%	.0003

The pattern for virology is similar to that for confirmed symptomatic flu. Influenza viral shedding is reduced by tamiflu prophylaxis with somewhat more than 10% fewer prophylaxed households having any contact with viral shedding than among control households. This secondary endpoint would have been statistically significant if one excluded all contacts with positive virology at baseline or if one were to pretend that individual contacts could be treated as independent.

3.1.2 Analysis of Symptom Duration

The FDA reviewer also attempted to replicate the applicant's results with respect to duration of influenza symptoms for those subjects who did get confirmed influenza. In the results presented here, onset of influenza was considered the earlier of the first day with either cough or nasal congestion, provided that fever >=37.8° C occurred then or within two diary cards or

the first day with fever, provided that cough or nasal congestion occurred then or within two diary cards. In either case, confirmation by virology was required. Duration (in days) of symptoms was defined as the difference between onset and the day of the first of two consecutive diary cards without any of fever, cough, or nasal congestion.

It appeared that tamiflu prophylaxis reduced the duration of the influenza episode for those subjects who contracted confirmed influenza. Table 3.1.2 A gives the number of subjects with confirmed flu and their mean duration of symptoms, as just defined, for both arms, the difference in mean durations for control minus prophylaxis and the 95% confidence interval for the difference, together with the p-value using a normal approximation. Results are given for the subjects with a community infection source (non-infected index case) and index case infection source, as well as for the Mantel-Haenszel weighted pooling of the two groups.

TABLE 3.1.2 A
DURATION OF CONFIRMED INFLUENZA EPISODES

	Mean	95%_Limits		Means		N's		
Source	Diff	Lower	Upper	Cont	Prop	Cont	Proph	P-value
Pooled	4.79	1.90	7.69	10.6	5.6	43	13	.0012
Commun	10.75	3.91	17.59	15.5	4.8	8	2	.0021
Index	3.65	0.47	6.84	9.5	5.8	35	11	.0247

Prior tamiflu prophylaxis appeared to reduce the duration of influenza symptoms by 3-4 days even if the prophylaxis failed. It should be noted that this analysis treated individual cases among contacts as if they were statistically independent and made no adjustments for the potential correlation among secondary cases within the same household. In fact, 33 of the 56 cases occurred as the single case in a household, 10 cases occurred in pairs within the same household, 9 cases occurred in triplets, and one household had 4 cases. Table 3.1.2 B shows the results on symptom duration by household, using the mean duration of all contact cases within a household as the symptom duration for the whole household. Results using the maximum of all cases in the household look similar and are not presented.

TABLE 3.1.2 B
DURATION OF CONFIRMED INFLUENZA EPISODES

	Mean	95% Limits		Means		N's		
Source	Diff	Lower	Upper	Cont	Prop	Cont	Proph	P-value
Pooled	6.05	2.62	9.48	11.6	5.5	30	12	.0005
Commun	8.30	0.13	16.47	13.1	4.8	5	2	.0466
Index	5.60	1.83	9.37	11.3	5.7	25	10	.0036

3.1.3 Missing Data

The FDA statistical reviewer surveyed the raw data set for missing diary cards among the contacts. Tables 3.1.3 A and B give a summary of the results. Table 3.1.3 A shows the percent of diary cards which lagged the preceding diary card by 1-12 hours, 13-18 hours, 19-24 hours, or >=25 hours. About 60% of diary cards occurred on schedule, within 12 hours of the previous one and over 95% occurred with 18 hours of the previous one.

TABLE 3.1.3 A
TIME LAGS BETWEEN SUCCESSIVE DIARY CARDS

LAGHOUR	TRT=P	TRT=T
1-12	61.4%	60.6%
13-18	95.6%	97.5%
19-24	98.7%	99.3%
25-106	100%	100%

Table 3.1.3 B shows the average difference between the number of diary cards with a report of severity or absence of nasal congestion, cough, and fever and the expected number of such cards if there had been two cards per day from the start of the study. Results are given separately for data prior to onset of flu and posterior to onset of flu, if flu occurred.

TABLE 3.1.3 B
DIFFERENCES BETWEEN OBSERVED AND EXPECTED
REPORTS OF SYMPTOMS

Arm		Symptom Nasal Cong.	Cough	Fever
Proph	Prior to Flu	-2.24 cards	-2.26	-2.16
	After Flu	-2.42	-2.35	-2.40
Control	Prior to Flu	-.56 cards	-.58	-.52
	After Flu	-2.43	-2.34	-2.42

It would not appear that missing data affects the conclusions of the study in any consequential way. Subjects seldom took more than 6 hours longer than desired to fill out their next diary card and only failed to make a report on symptoms about one day (two cards) during the period prior to onset of flu or end of the study.

3.2 Evaluation of Safety

This drug has already been approved both for treatment and for prophylaxis in adults and adolescents. The current submission merely extends the prophylaxis indication to younger children. There are no new safety issues in this trial that would raise concerns not addressed in the earlier submissions.

4. Results in Special Populations

4.1 Gender, Race, and Age

Tables 4.1 A and B give the differences in incidence of confirmed influenza and of viral shedding by sex, age category, and race. As in tables 3.1.1 A and B above, each line of the table gives the level of the covariate, the incidence rate for control and prophylaxed arms, the difference and 95% confidence limits on the difference and the two-sided p-value for the difference (using a z approximation for both confidence levels and p-values).

TABLE 4.1 A
INCIDENCE OF CONFIRMED FLU
BY SEX, RACE, AGE

	Mean	95% Limits		Control	Prophyl	
Covariate	Diff	Lower	Upper			P-value
SEX						
Female	6.2%	1.9%	10.6%	19/213=9%	6/223=3%	.005
Male	8.9%	3.6%	14.2%	21/179=12%	5/177=3%	.001
RACE						
Asian	-1.9%	-13.2%	9.4%	1/32=3%	1/20=5%	.75
Black	19.2%	4.1%	34.4%	5/26=19%	0/32=0%	.013
White	7.3%	3.6%	11.0%	34/333=10%	10/344=3%	.0001
AGE						
1-4	8.9%	-16.0%	33.8%	3/15=20%	2/18=11%	.48
5-11	14.0%	3.4%	24.7%	17/81=21%	5/72=7%	.01
12-17	4.9%	-3.2%	12.9%	6/68=9%	3/76=4%	.23
18-64	5.9%	2.6%	9.3%	14/220=6%	1/224=0%	.0005
>=65	0%	.	.	0/8=0%	0/10=0%	.

One can see a consistency of results across both sexes, all races, and all age categories except the 1-4 year olds. The latter category is the smallest of the groups and the true difference in incidence rates is highly uncertain with anything from a 28% inferiority to a 21% superiority being plausibly compatible with the data. The data certainly support the conclusion of prophylactic efficacy down to an age of 5 years.

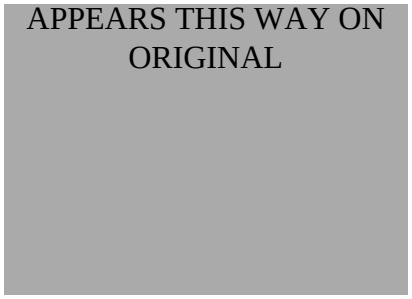
TABLE 4.1 B
VIRAL INCREASE
BY SEX, RACE, AGE

Covariate	Mean Diff	95% Limits Lower	Upper	Control	Prophyl	P-value
SEX						
Female	7.6%	0.0%	15.2%	53/215=25%	38/223=17%	.049
Male	14.3%	6.8%	21.8%	42/180=23%	16/177=9%	.0002
RACE						
Asian	6.9%	-14.3%	28.1%	7/32=22%	3/20=15%	.53
Black	31.9%	10.0%	53.9%	12/27=44%	4/32=13%	.0044
White	9.0%	3.3%	14.8%	76/335=23%	47/344=14%	.0022
AGE						
1-4	21.5%	-9.5%	52.5%	7/16=44%	4/18=22%	.17
5-11	13.0%	-1.3%	27.3%	30/82=37%	17/72=24%	.076
12-17	5.1%	-8.2%	18.4%	16/68=24%	14/76=18%	.45
18-64	10.5%	4.2%	16.9%	42/221=19%	19/224=8%	.0011
>=65	0%	.	.	0/8=0%	0/10=0%	.

The pattern for positive virology is similar to that for virally confirmed symptomatic flu: there is an estimated prophylactic efficacy across ages, sexes, and races; with the possible exception of children 1-4.

We omit any results with symptomatic flu since those should be a mixture of true flu, where efficacy is established by table 4.1 A and symptoms falsely resembling flu, where efficacy would not be expected.

There were no other baseline covariates collected that would permit analysis stratified other potentially interesting subgroups. One may consult prior reviews of this product for results on efficacy stratified by covariates other than age, race, and sex. Those reviews did not raise concerns that tamiflu might be less effective in particular identifiable subgroups.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5. Statistical Reviewer's Conclusions

In conjunction with a prior submission, the applicant has established that tamiflu, used in 30-75 mg qd (depending on age) for 10 days was effective as a prophylactic against influenza when prophylaxis was started promptly after the diagnosis of a family member with influenza. The risk of at least one new member of the family contacting influenza from 22% with only the index case being treated to 5% with prophylaxis. Measured on an individual basis, the risk was reduced from 11% to 2%. Even the index case were not infected, the prophylaxis was effective in reducing the risk of community acquired influenza from 5% to 2%.

This pattern was consistent across ages, with reduction in risk for the youngest subjects being from 20% to 11% for those under the age of 5 and from 19% to 7% for those under the age of 12.

There was also an apparent reduction of 3-4 days in the duration of symptoms for those subjects who did contact influenza despite prophylaxis.

The results were consistent across age group, sex, and race.

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Soon

cc:
Archival NDA #21-246

HFD-530
HFD-530/Dr. Birnkrant
HFD-530/Dr. Murray
HFD-530/Mr. O'Neil
HFD-530/Dr. Lewis
HFD-725/Dr. Hammerstrom
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21246/S-017

MICROBIOLOGY REVIEW(S)

Microbiology Review
Division of Antiviral Products (HFD-530)

NDA: 21-246 **Serial No**. SE5-017 **Reviewer**: N. Battula, Ph.D.
NDA: 21-087 **Serial No.** SE5-030

Date submitted: April 15, 2005 **Date received**: April 18, 2005
Date assigned: April 22, 2005 **Date reviewed**: December 15, 2005

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

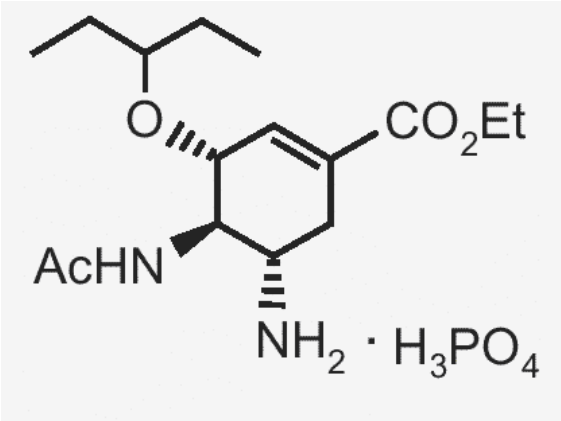
Product names: Proprietary: Tamiflu®
Nonproprietary: Oseltamivir phosphate
Code: Ro 64-0796

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

Empirical formula: $C_{16}H_{28}N_2O_4$ (free base)

Molecular weight: 312.4 for oseltamivir free base and
410.4 for oseltamivir phosphate salt

Structural formula:



Dosage form: Oral, capsules strength 75mg (free base equivalent) and solution

Indication: Prophylaxis of influenza A and B infection in households for patients ≥1 year of age

Related documents: NDAs 21-246 and 21-087, and IND 53093

Microbiology Review
Division of Antiviral Products (HFD-530)

NDA: 21-246 **Serial No**. SE5-017 **Reviewer**: N. Battula, Ph.D.
NDA: 21-087 **Serial No.** SE5-030

BACKGROUND and SUMMARY: On October 27, 1999, Hoffmann-La Roche Inc. received approval for Tamiflu® capsules (NDA # 21-087) for the treatment of uncomplicated acute illness due to influenza infections in adults who have been symptomatic for no more than two days. On November 17, 2000, Hoffmann-La Roche Inc. received approval for Tamiflu® capsules (NDA # 21-087 SE1-002) for the prophylaxis of influenza in adults and adolescents of 13 years and older. On December 14, 2000 Hoffmann-La Roche Inc. received approval for Tamiflu® oral suspension (NDA # 21-246) for the treatment of uncomplicated acute illness due to influenza infections in patients older than one year of age who have been symptomatic for no more than 2 days.

Hoffmann-La Roche Inc. submitted the current efficacy supplement NDA 21-246/SE5-017 to extend the Tamiflu® indication for the prophylaxis of influenza virus A and B infection in pediatric patients 1 to 12 years of age. In support of the requested indication the applicant provided safety and efficacy study reports from protocol WV16193. Protocol WV16193 is a multinational, randomized, open-label study of Tamiflu® for the management of influenza in households. In the study the entire households were offered entry and the index cases received treatment with oseltamivir phosphate[1]. Household contacts were randomized (by household) to receive either once-daily prophylaxis with oseltamivir for 10 days (Group P) or receive treatment for 5 days upon the emergence of influenza-like illness (Group T). The primary end point of the study was the incidence of laboratory confirmed clinical influenza during the 10 day period following onset of symptoms in the index case. For protocol details and evaluation of the efficacy and safety of the study, please see the clinical review by Dr. Linda L. Lewis and the statistical review by Dr. Thomas Hammerstrom. The following microbiology review primarily deals with influenza viral resistance data in the study WV16193.

In the clinical trial WV16193, prophylaxis and concurrent treatment and re-treatment within contacts was done with oseltamivir phosphate. In this setting the potential exists for the emergence of resistance against oseltamivir in the influenza virus in patients receiving treatment and subsequent transmission of resistant virus to those receiving prophylaxis. It is expected that there would be no protective effect of the drug against resistant virus in those taking the drug prophylactically. To evaluate the potential generation and transmission of oseltamivir resistant virus in such settings the applicant assessed the susceptibility of influenza virus isolates from the study subjects.

[1] Oseltamivir phosphate is the ester prodrug that requires hydrolysis for conversion to the active form Oseltamivir carboxylate. In clinical studies the prodrug is administered and for neuraminidase enzyme phenotyping assay studies the active form of the drug oseltamivir carboxylate is used.

In the study 274 households were recruited. The first members of the household presenting with influenza-like illness (index case) were treated for 5 days with oseltamivir phosphate; 75 mg capsules bid for adults and depending on the age 30, 45 or 60 mg bid suspension for children. The households were then randomized to either of the prophylaxis group or the treatment group. In the prophylaxis group, contacts of the index case were given oseltamivir phosphate for 10 days, 75 mg q.d. for adults, and 30, 45 or 60 mg for children depending on age. In the treatment group, the contact cases were treated with oseltamivir phosphate upon presentation with influenza-like illness in the same way as the index cases, 75 mg of oseltamivir phosphate bid for 5 days.

To collect influenza virus samples from the study subjects, nose and throat swabs were taken from all household members on presentation of the index case with influenza-like symptoms (baseline sample). Swabs were taken again from the index cases on day 6 because previous studies showed that on the last treatment day the resistant virus most likely emerges. Swabs were also collected from all contacts on day 10. Details of the methodology for virus sample collection, storage, virus expansion and neuraminidase enzyme assays were described in the original microbiology review (NDA 21-087) for adult treatment, and in the NDA 21-264 for treatment of pediatric patients. Briefly, using an aliquot of the swab sample, virus was expanded for 7-days in MDCK cell culture. The virus cultures were tested for influenza virus A or B positivity by immunofluorescence. Influenza viral neuraminidase activity and its inhibition by oseltamivir carboxylate were determined using the virus samples from the culture supernatants. The enzyme assays were carried out in (b) (4) . Results are expressed as the inhibitory concentration (IC_{50}) which is the concentration of inhibitor necessary to reduce the neuraminidase activity by 50% relative to the enzyme activity containing no inhibitor.

According to the applicant, the IC_{50} values for the inhibition of neuraminidase enzyme activity could be determined in 155 virus samples collected from 145 patients (Appendix 1 of research report No. 1009157). Sixty nine of these patients were adults and 76 were children aged 12 or under. One hundred and four patients were index cases and 41 patients were household contact cases. Seventy of the patients (index and contact) were infected with influenza A virus, and 67 patients were infected with Influenza B. Three patients (1 index and 2 contacts) were dually infected with influenza A/B. Infection of contacts could be the result of infection from the index case prior to treatment of the index case, infection after treatment of the index cases (possible transmission of resistant virus), and/or infection from outside the household, some of which may be of an influenza type discordant with the index case, information regarding the discordant

influenza virus infections between the index and contact cases are listed in appendices 1 and 3. Analysis of the tables shows that 3 contacts were infected with influenza B when 93 index cases were infected with influenza A, and 2 contacts were infected with influenza A when 43 index cases were infected with influenza B. Five of the 41 contact cases (12%) were discordant indicating infection from a source outside of the household. The applicant did not carry out genotyping of the virus isolates to identify the source of the other non-discordant contact infections.

The neuraminidase IC_{50} values for all of the virus isolates from patients ranged from 0.9 nM to 10.6 nM for influenza virus A and the range was 23.5 nM to 177.5 nM for influenza virus B. This difference in the IC_{50} values between influenza virus A and B are consistent with the previous studies on the IC_{50} values of laboratory and clinical isolates which showed that the IC_{50} values for influenza virus B neuraminidase inhibition were higher than for influenza virus A.

Baseline and post-treatment matched pair virus samples were obtained for 10 patients for the neuraminidase phenotyping assay. Four of the 10 matched pairs were from index case, one patient infected with influenza virus A and 3 patients infected with influenza virus B. Five of the 10 patients were contact cases infected with influenza virus B, four on the treatment arm and one from the prophylaxis arm. With regard to the remaining matched pair (patient 0150) the applicant is uncertain about the coding and it may be a duplicate of baseline sample and the patient was excluded from the total of matched pair analysis.

Table 1. Viral neuraminidase IC_{50} values for matched pairs in study VW16193

Patient	**Index case or Contact case**	**NA IC_{50} nM[@]**		**Influenza virus type**
		Baseline	**Post-Txt**	
5700	Index	3.8	1.8	A
0717	Index	62.8	53.3	B
4851	Index	49.4	177.5	B
4853	Index	43.2	51.2	B
4738	Contact	46.8	87.9	B
6610	Contact	142.2	30.6	B
6611	Contact	151.8	125.5	B
6612	Contact	83.4	65.6	B
6578[#]	Contact	4.8	143.8	B
0150	Contact	50.4	54.0	A/B

@ Neuraminidase IC_{50} values at baseline and post treatment

This matched pair at baseline was influenza A and at post treatment was influenza B

Neuraminidase inhibition by oseltamivir carboxylate expressed in terms of IC_{50} values for all of the samples (n=155) in the study WV16193 ranged from 1 to 12 fold for influenza A virus (0.9 nM to 10.6 nM), and 1 to 8 fold (23.5 nM to 177.5 nM) for influenza B virus. The median baseline and post-treatment IC_{50} values for the 3 matched influenza B index samples presented in Table 1 were 49.4 nM and 53.3 nM, and for the 5 matched influenza B contact samples, 83.4 nM and 87.9 nM, respectively. This difference in neuraminidase assay phenotype between the index and contact cases would be consistent with the transmission of resistant virus; however, the small number of samples and the lack of an established relationship between neuraminidase assay values and in vivo susceptibility preclude forming a definitive conclusion. Genotypic analysis comparing the baseline and end of treatment HA and NA genes may have resolved this issue. A large shift in the IC_{50} value for the isolates from contact patient 6578 was found. Interestingly, the first isolate was influenza A and the second influenza B. According to the sponsor, the different influenza types were the result of a mixed infection; however, this result could be due to a sample collection or laboratory error. The results suggest that in this study with few matched isolates (n=9) there was neither emergence of resistance virus in the treated patients nor transmission of resistant virus to contact cases. Based on these limited data the applicant stated that in this study there is no evidence for the presence of resistance neuraminidase phenotype. It is to be noted however that several previous clinical studies that the applicant conducted in support of Tamiflu® use in adult and pediatric patients for the treatment and prophylaxis indication provided a larger data set showed the emergence oseltamivir resistance in influenza virus. The current Tamiflu® package insert shows the emergence of resistance of 1.3% (4/301) in adults and adolescents and 8.6% in pediatric patients aged 1-12 years of age. Roche calculated a lower resistance rate (4.0%) in the pediatric patients which was different than that in the current label. In the calculation, Roche chose to use a different denominator than that used in the adult studies. In the pediatric cases Roche included in the denominator the patient numbers when the virus cannot be cultured in post-treatment sample assuming that these patients did not carry resistant virus. FDA used pre-and post-treatment matches only as was done for the adult calculation to arrive at the resistance rates. The small number of total neuraminidase samples (n=155) and the smaller number of matched samples (n=9) may be too small to reveal the emergence of resistance in study WV16193. A recent study of the rate of oseltamivir resistance in Japanese children found a rate of 18% (1). The higher rate of resistance observed in this study may be due to the different

dosing recommendations in Japan or to a virus with a different genetic background more favorable to the development of resistance to oseltamivir.

In this submission, the applicant addressed the effect of oseltamivir resistance conferring neuraminidase mutations, E119V, H274Y and R292K, which have emerged in clinical studies and have any effect on the antigenic properties of neuraminidase. Influenza virus neuraminidase is a bifunctional enzyme in that it acts both as an enzyme by removing sialic acids from glycoproteins and also as a major antigenic determinant. In the neuraminidase protein, four antigenic sites each consisting of multiple epitopes has been recognized. The applicant compared the antigenicity profiles of oseltamivir sensitive isolates with resistant isolates containing mutations in the neuraminidase. The resistant isolates were found to be not antigenically different from the non-resistant wild-type pretreatment virus isolates. The results suggest that the catalytic activity domain and the antigenic domains of neuraminidase are distinct non-interacting entities and. the oseltamivir resistant virus isolates retain wild-type antigenicity.

The envelope glycoproteins hemagglutinin and neuraminidase of influenza virus function in a complementary manner in the life cycle of the virus. Influenza virus hemagglutinin recognizes and binds to the host cell sialic acid (neuraminic acid) receptors and the neuraminidase activity release the virus from receptor sialic acid, thereby promoting the virus release. Because of the molecular interaction between the hemagglutinin and the neuraminidase proteins, it is conceivable that drugs that target viral neuraminidase may also induce resistance in both the neuraminidase and hemagglutinin. In studies previously reported, the applicant evaluated the emergence of resistance mutations in the hemagglutinin using pre- and post-treatment sample sets. The analysis involved the nucleotide sequencing of the entire HA1 region, which also contains the sialic acid binding site. A total of 150 patients samples have been sequenced. It was found that the incidence of nucleotide variants was the same between the placebo and oseltamivir treated groups. The data set showed no uncommon variants more than once. Thus it was concluded that there were no oseltamivir related mutations in the viral hemagglutinin and the variants seen in the hemagglutinin gene are random in nature.

CONCLUSIONS and RECOMMENDATIONS: The efficacy supplement submitted in support of the extension of the Tamiflu® indication for prophylaxis of influenza virus A and B infection in pediatric patients of 1 to 12 years of age provided neuraminidase phenotype in the index and treated cases. The combined data in this single study with a small set of matched samples (N=9) showed no emergence of resistance to oseltamivir. However, several other clinical trials that the applicant conducted in support of the

treatment and prophylaxis indications in adults and children showed the emergence of resistance and the current package insert for Tamiflu® reflects the resistance information.

Published reports (1, 2) also show that treatment of influenza virus infections with Tamiflu® results in the emergence or resistance at higher rates (18%) in children than that found in Roche conducted clinical trials in children. In addition there is one report (3) in which a patient infected with influenza strain H5N1 and treated with oseltmivir phosphate developed a resistance mutation at position H274Y in the viral neuraminidase. Thus the emergence of resistance against Tamiflu® in influenza virus is a reality to be reckoned with. The clinical and epidemiological consequences of neuraminidase resistant virus in humans remains to be seen.

To shed some light on the efficiency of infectivity, replication capacity, and pathogenicity of the oseltamivir resistant virus, the applicant previously conducted studies with drug-sensitive and clinically derived drug-resistant influenza virus with point mutations (E119V, H274Y and R292K) in the ferret animal model. Based on the ferret animal model, study the applicant concluded that infectivity, replication capacity of the mutant virus was severely compromised (details of the animal model data are in the Tamiflu® microbiology review NDA 21-246). The claimed crippling effects of oseltamivir resistant influenza virus observed in animal studies have not yet been shown in human.

It is believed that some neuraminidase inhibitor resistant viruses might become part of the circulating viral population when neuraminidase inhibitors are widely used in the general population. To address the issue of emergence of neuraminidase inhibitor resistant influenza virus in the general population and evaluate the clinical significance and epidemiological consequences of resistant virus strains, an independent international body, the Neuraminidase Inhibitor Susceptibility Network (NISN), consisting of pharmaceutical companies, senior academic influenza experts and WHO representatives for each of the four influenza centers (Australia, Japan, UK and USA) was formed (3, 4). The NISN appears to have determined the susceptibilities of a large number influenza virus isolates circulating worldwide before the introduction of neuraminidase inhibitors (1997-1999) and post-licensure and usage over 3-5 years. The results are expected to be made public soon which will shed additional light on the emergence of resistance to oseltamivir and other neuraminidase inhibitors.

Microbiology Review
Division of Antiviral Products (HFD-530)

NDA: 21-246 **Serial No**. SE5-017 **Reviewer**: N. Battula, Ph.D.
NDA: 21-087 **Serial No.** SE5-030

There are no microbiology concerns in this efficacy supplement for the indication of Tamiflu® for prophylaxis of influenza virus A and B infection in pediatric patients of 1 to 12 years of age. The supplement for use of Tamiflu® in prophylaxis of influenza virus infection is recommended for approval.

_____
Narayana Battula, Ph.D.
Microbiologist

Concurrence:

HFD 530/ Assoc Dir. _____Date _____

HFD 530/TLMicro. _____ Date _____

RFERENCES:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21246/S-017

OTHER REVIEW(S)

M E M O R A N D U M

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

ODS PID# D050502

DATE: December 16, 2005

FROM: Evelyne T. Edwards, Pharm.D., M.A., Post Marketing Safety Evaluator
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THROUGH: Rosemary Johann-Liang, M.D., Deputy Director
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Division of Drug Risk Evaluation
Office of Drug Safety (ODS)

TO: Debra b. Birnkrant, M.D., Division Director
Division of Anti-Viral Products (DAVP)
Office of Antimicrobial Products (OAP)

SUBJECT: Post-Marketing Adverse Event Reports Review of serious skin/soft tissue disorders, anaphylaxis, renal toxicity, hepatic toxicity, and central nervous system/psychiatric disorders associated with the use of Tamiflu®.
Drug: Oseltamivir phosphate
NDAs: 21-087 (Tamiflu® Capsules), 21-246 (Tamiflu® Oral Suspension), Roche

1. EXECUTIVE SUMMARY

The purpose of this consult is the review of specific adverse events reported from the postmarketing experience with Tamiflu® (oseltamivir). A recent one-year post pediatric exclusivity review[1] of adverse events with oseltamivir identified two specific safety issue requiring further evaluation, neuropsychiatric events and hypersensitivity reactions including anaphylaxis and serious skin reactions. These and other serious adverse events of concern, renal toxicity and hepatic toxicity, were included for review because of postmarking reports identified during the 2004-2005 influenza season and to supplement the Tamiflu® (oseltamivir) efficacy supplements (NDA 21-246/SE5-017 and NDA 21-087/SE5-030) to extend the prophylaxis indication to patients 1-12 years of age currently under review by the DAVP.

[1] Edwards, Evelyne: Tamiflu®(oseltamivir), One-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review. Aug 2005

Hepatic and Renal Toxicity
A search of FDA's Adverse Event Reporting System (AERS) identified 21 cases of hepatic toxicity (including 14 cases of hepatic failure) and 43 cases of renal toxicity (including 18 cases of renal failure) with a serious outcome. These cases are confounded by other risk factors and concomitant medications and no sentinel case of liver or renal toxicity was identified in these case series that can be solely related to oseltamivir. Because a clear association could not be determined based upon the current case series, we do not recommend that hepatic failure/fulminant hepatitis or renal failure/impairment be added to the oseltamivir label at this time. We will continue to monitor postmarketing cases and discuss with DAVP in a timely manner as reports become available.

Neuropsychiatric Events
Pediatric neuropsychiatric adverse events were one topic of discussion at a November 18, 2005 Pediatric Advisory Committee (PAC). A disproportionate number of these reports are from Japan and a subset of the reports described patterns of abnormal behavior that were especially concerning. CDER concluded and the PAC agreed that US adverse event reports do not show comparable CNS effects in the pediatric age group as seen in the Japanese data and that CDER should continue to closely monitor these events.

To complement the pediatric review and further investigate this issue, the AERS database was search for neuropsychiatric events with all ages; 126 (3 fatal and 123 non-fatal) unduplicated reports were identified. It is difficult to adequately assess a clear relationship of these neuropsychiatric events to the use of oseltamivir for multiple reasons. First, the majority of the reports are foreign making it harder to capture an accurate description of an adverse event because of difficulties associated with the direct translation of medical events. Additionally, the narratives in domestic reports often do not provide adequate information to assess a clear relationship. Finally, many of these events such as delirium, convulsions, and depressed consciousness are also associated with influenza making it difficult to distinguish between symptoms that are a manifestation of influenza and potential adverse effects of oseltamivir. Although, no clear association between the neuropsychiatric events and oseltamivir can be determined at this time, the subset of 17 cases of "abnormal behavior" (including two reports of death) remains a source of concern. Our continuing concern is due to the particularly striking nature of these reports that is uncharacteristic of our usual clinical experience with influenza encephalopathy. We are uncertain at this time if there is a possible drug-disease contribution to these adverse event reports.

As oseltamivir is used globally on a large scale, we may potentially see more reporting from other geographical regions (i.e. US and European) where the data collected from different populations may provide useful information for further analysis as to whether these neuropsychiatric events are drug-related or manifestations of the underlying disease, or a combination of drug-disease expression. We will continue close monitoring of these neuropsychiatric events and will communicate any findings to the reviewing division in a timely manner as reports become available.

Hypersensitivity Reactions
A review of the postmarketing safety data from the AERS database identified 43 unduplicated cases of serious skin events for further review. The majority of the reports were from Japan (34/43); 7 reports were from the US, then one each from Australia and France. There were 16 pediatric patients from 0 – 16 years of age. Among these 43 cases, there are 24 cases of Stevens-Johnson syndrome (SJS), 14 cases of erythema multiforme (EM), four cases of toxic epidermal necrolysis (TEN), and one case of pemphigus.

The majority (56%, 24/43) of the serious skin reactions were classified as having a high probability of being associated with the use of oseltamivir based on the following criteria:

1. There was a temporal relationship between the occurrence of the adverse event and the use of oseltamivir.
2. Oseltamivir was the only drug introduced at the time of the event.
3. Serious skin reactions are typically not associated with influenza disease; and
4. Serious skin reactions are typically associated with drugs.

Many cases also required patients be hospitalized and receive supportive treatment (i.e. steroids, antihistamines) for their serious skin adverse events.

In addition to the serious skin reactions, 75 other hypersensitivity reactions including anaphylactic reactions-6, anaphylactoid reactions-6, and anaphylactic shock-17 have been reported in the literature and in the post-marketing reporting with 12 of these 75 cases considered probably related to the use of oseltamivir. These adverse events are serious and can be life-threatening resulting in hospitalization for supportive treatment with steroids, antihistamines and dopamine.

We recommend the addition of hypersensitivity reactions to the oseltamivir label to highlight these serious postmarketing reports associated with the use of Tamiflu and alert patients to seek timely and appropriate treatment if a hypersensitivity reaction occurs or is suspected. We also believe that an appropriate method to communicate this safety-related message is a statement in the **Precautions** section of the label**.** The following is possible wording for your consideration.

"Hypersensitivity Reactions: Anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported in post-marketing experience with TAMIFLU. TAMIFLU should be stopped and appropriate treatment instituted if an allergic-like reaction occurs or is suspected."

And, under ADVERSE REACTIONS section, Observed During clinical Practice sub-section, the following statement should also be added: "*Dermatologic: dermatitis, eczema, rash, urticaria, Stevens - Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis (see PRECAUTIONS)."*

Table of Content

2. REASON FOR REQUEST/REVIEW

DAVP requested a postmarketing review of serious neuropsychiatric adverse events, serious skin/soft tissue disorders, renal toxicity, and hepatic toxicity after postmarking reports were identified during the 2004-2005 influenza season. This review evaluates the reports in all ages since the approval date.

3. AERS SEARCH RESULTS

3.1 Search Date: 08-29-2005

3.2 Search Type: [x] AERS [x] Literature [ ] Other

3.3 Search Criteria:

Drug Name: Tamiflu® (oseltamivir phosphate)

MedDRA Terms:

1. ODS LIVER FAILURE/CIRRHOSIS:
   a. HLT Hepatic Failure and Associated Disorders including the following 6 PTs:
      Asterixis, coma hepatic, hepatic encephalopathy, hepatic failure, hepatorenal failure, hepatorenal syndrome.
   b. HLT Hepatic Fibrosis and Cirrhosis including the following 11 PTs:
      Biliary cirrhosis, biliary cirrhosis primary, biliary fibrosis, cardiac cirrhosis, cirrhosis alcoholic, congenital hepatic fibrosis, cryptogenic cirrhosis, hepatic cirrhosis, hepatic fibrosis, lupoid hepatic cirrhosis, nodular regenerative hyperplasia.
   c. PT hepatic necrosis, hepatic fulminant, liver transplant.

2. ODS RENAL FAILURE:
   PT dialysis, haemodialysis, peritoneal dialysis, renal transplant, acute prerenal failure, anuria, diabetic end stage renal disease, hepatorenal failure, hepatorenal syndrome, oliguria, renal failure acute, renal failure chronic, renal failure neonatal, renal failure, neonatal anuria, haemolytic uraemic syndrome, pancreatorenal syndrome, postoperative renal failure, postrenal failure.

3. NEUROPSYCHIATRIC
   a. HLT Suicidal and Self-injurious Behavior including the following 7 PTs:
      Complete suicide, intentional self-injury, suicidal ideation, suicide attempt, self-injurious ideation, self-injurious behavior, self mutilation.
   b. PT abnormal, abnormal dreams, agitation, anxiety, cognitive disorder, confusional state, convulsion, delirium, delusion, delusional perception, depressed level of consciousness, disturbance in attention, encephalitis, encephalopathy, excitability, fear, hallucination, hallucination auditory, hallucination visual, hallucination mixed, illusion, loss of consciousness, mania, mental impairment, nervousness, panic attack, panic reaction , restlessness, schizophrenia, thinking abnormal.

4. ODS SERIOUS SKIN:
   a. HLT Bullous Conditions including the following 16 PTs:
      Acquired epidermolysis bullosa, application site vesicles, benign familial pemphigus, blister, blood blister, bullous impetigo, cervical bulla, dermatitis bullous, dermatitis herpetiformis, diabetic bullosis, epidermolysis, epidermolysis bullosa, erythema multiforme, herpes gestationis, implant site vesicles, injection site vesicles, linear IgA disease, lip blister, oculomucocutaneous syndrome, Pemphigoid, penile blister, porphyria non-acute, pseudoporphyria, staphylococcal scalded skin syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis.
   b. PT Acute generalized exanthematous pustulosis

5. ANAPHYLAXIS, HYPERSENSITIVITY, ANAPHYLACTIC/ANAPHYLACTOID REACTIONS:
   a. PT drug hypersensitivity, hypersensitivity, immune system disorder, swelling face, type I hypersensitivity.
   b. HLT Anaphylactic responses including the following 4 PTs:
      Anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock.
   c. HLT Angioedemas including the following 12 PTs:
      Angioneurotic oedema, eyelid oedema, face oedema, herediatary angioedema, Laryngeal oedema, laryngotracheal oedema, oedema mouth, periorbital oedema, tongue oedema, small bowel angioedema, circumoral oedema, oculo-respiratory syndrome.

4. LIVER FAILURE/CIRRHOSIS EVENTS

4.1 Relevant Tamiflu® Labeling for Liver Failure/cirrhosis Events

The current labeling contains the following terms related to liver adverse events under ADVERSE REACTIONS/Observed During Clinical Practice for Treatment/Digestive: hepatitis and liver function tests abnormal.

4.2 Search results (n = 21)

There were 24 reports of ODS-LIVER FAILURE/CIRRHOSIS adverse events associated with the use of Tamiflu® (oseltamivir phosphate) in AERS. All 24 reports were manually reviewed. **Twenty-one** unduplicated cases were identified and reviewed for this consult.

4.3 Summary of Data (n = 21)

Demographics:

Age: n = 20
Mean = 51 years
Median = 56 years
Range: 10 to 83 years of age
0 – 16 years: n = 1
17 – 89 years: n = 19

Sex: n = 21
Male = 13
Female = 8

Location: US– 9, Japan – 9, and Germany – 3,

Outcomes:
Death – 9, Life-threatening – 5, Hospitalization – 4, Other/Medically Significant – 3.

Types of AE:
Hepatic failure: n = 14
Hepatic fulminant: n = 4
Hepatic Necrosis: n = 2
Hepatic fibrosis/steatosis: n = 1

Time to onset:
Range: 2 – 10 days
Mean: 5 days

4.4 Discussion

Dipiro JT et al[2] stated that "the number of drugs associated with adverse reaction involving the liver is extensive. The overall incidence of human liver injury from most drugs is fortunately very low. Chronic liver disease and cirrhosis collectively account for approximately 1% of annual mortality in the United States. Alcohol-induced liver disease accounts for most of these deaths. Still, for an individual patient, drug-induced liver disease is usually a profound, life-changing disease. The liver's function affects almost every other organ system in the body."

Among the 21 reports, there are nine fatalities. Five cases are from Japan, three from the US and one from Germany. One report (**Case # 3924464)** was incorrectly coded as "life-threatening (LT)" for its outcome; the sponsor has been requested to submit a follow-up report to add "LT" to the "death" outcome as originally reported instead of changing "the seriousness criteria from fatal to life threatening" as noted in the first follow-up report. The nine patients who experienced fatal liver failure and/or fulminant hepatitis had either a prior history of liver transplant (1), lung transplant (1), splenectomy (1), pulmonary tuberculosis (1), hepatic cirrhosis (1) and/or having concurrent pneumonia/infections (5). All transplant patients are at increased risk of opportunistic infections, and the risk increases as they are also on immunosuppressive agents like mycophenolate mofetil or tacrolimus. In addition, these nine patients were concomitantly taking clarithromycin, haloperidol, acetaminophen, sulbactam, or sulfamethoxazole/trimethroprim, all of which have been associated with liver function abnormalities. Even though all nine patients had received oseltamivir therapy prior to their fatal outcome, their death appeared to be the end result of the progression of their end-stage disease and sepsis.

The remaining 12 cases of non-fatal liver adverse events included three cases of fulminant hepatitis and six cases of hepatic failure. The three cases of fulminant hepatitis involved young adults of 18, 21, and 37 years old, respectively. Two patients had concurrent hepatitis B and one of these two patients had reported chronic alcohol use. The third case has very limited information except for the reported adverse event during the use of oseltamivir. Again, this group of 12 patients can only be classified as *possibly related* to the use of oseltamivir because these cases are confounded by risk factors such as prior medical history of hepatitis A, hepatitis B, hyperlipidemia (2), long-term alcohol consumption (2), concurrent suspect or active infection, and use of the following concomitant medications that have

[2] Dipiro JT et al. Drug-Induced Liver Disease. *Pharmacotherapy: A pathopysiologic Approach. Fourth Edition. McGraw-Hill.3*6:628-35

known reported liver dysfunction activities: diclofenac, ibuprofen, acetaminophen, levofloxacin, clarithromycin, and HMG-CoA reductase inhibitors. Two cases have very limited information except for the reported liver failure event; one patient had concurrent multi-organ failure and sepsis with an unknown outcome.

4.5 Summary

It does not appear that there is a sentinel case of severe liver toxicity (i.e. liver failure or fulminant hepatitis) among the 21 cases reviewed that could be solely related to oseltamivir therapy. These cases are confounded by other risk factors and concomitant medications. Therefore, we do not recommend adding hepatic failure or fulminant hepatitis to the oseltamivir label at this time.

5. RENAL FAILURE EVENTS

5.1 Relevant Tamiflu® Labeling for Renal Failure Events

Oseltamivir is not currently labeled for renal insufficiency or renal failure. However, oseltamivir is converted to oseltamivir carboxylate that is eliminated entirely (>99%) by renal excretion and dose adjustment is recommended in patients with serum creatine clearance of <30mL/min.

5.2 Search Results (n = 46)

There were 60 reports of ODS-RENAL FAILURE adverse events associated with the use of Tamiflu® (oseltamivir phosphate) in AERS. All 60 reports were manually reviewed. Four reports were excluded because the acute renal failure occurred before therapy with oseltamivir was started (2) or the patients did not experience a renal adverse event (2). **Forty-six** unduplicated cases were identified and reviewed for this consult.

5.3 Summary of Data (n = 46)

Demographics:

Age: n = 43
Mean = 52 years
Median = 52 years
Range: 4 to 92 years of age
< 60 years: n = 29
≥ 60 years: n = 14

Sex: n = 44
Male = 32
Female = 12

Location: Japan –25, and US – 13, Canada-3, Germany-3, France-1, and United Kingdom-1

Outcomes:
Death – 6, Life-threatening – 12, Hospitalization – 14, Diability-2, Required Intervention-1, Other/Medically significant – 11

Types of AE:
Acute renal failure (ARF): n = 23
Renal failure n = 15
ARF with renal tubular necrosis: n = 2
Oliguria/anuria: n=3
Rhabdomyolysis with ARF: n = 1
Renal Disorder: n=1
Hepatorenal syndrome: n=1

5.4 Summary

The majority of patients in this cases series had confounding variables (i.e. dehydration, concomitant medications[NSAIDS]) to the development of renal insufficiency besides the use of oseltamivir and a sentinel case of severe renal toxicity (i.e. renal failure) was not identified among the 46 cases reviewed that could be solely related to oseltamivir therapy. Therefore, we do not recommend adding renal impairment or renal failure to the oseltamivir label at this time. However, because oseltamivir is almost completely eliminated by renal excretion and dose adjustments are recommedned in patients with renal impairment we will continue to monitor AERS cases of renal insufficiency.

6. NEUROPSYCHIATRIC EVENTS

6.1 Relevant Tamiflu® Labeling for Neuropsychiatric Events

The current labeling contains the following terms related to neuropsychiatric adverse events under ADVERSE REACTIONS section; Observed During Clinical Practice for Treatment section; Neurologic: Seizure and confusion.

6.2 Search Results (n = 126)

There were 190 reports of neuropsychiatric adverse events associated with the use of Tamiflu® (oseltamivir phosphate) in AERS. The AERS search included 37 PTs (Section 3.3), which were also provided to Roche on August 30, 2005 for use in a requested safety analysis. All 190 reports were manually reviewed, and 180 unduplicated cases were identified of which 54 report (17 fatal and 37 non-fatal) were excluded from further discussion; see APPENDIX A for a list of reasons for all exclusions.

The remaining **126** neuropsychiatric adverse event reports were reviewed for this consult.

6.3 Summary of Data (n = 126)

Demographics:

Age: n = 122
Mean = 32.2 years
Median = 17 years
Range: 0.8 to 94 years of age
0 – 16 years: n = 59
17 – 94 years: n = 67

Sex: n = 125
Male = 70
Female = 55

Location:
Japan – 94 (75%), US – 24 (19%), Canada – 3, UK – 2, Germany – 2, and France – 1,

Outcomes:
Death – 3 (Japan), Life-threatening – 4, Hospitalization – 50, Required intervention – 2, Disability – 5, Other/Medically significant – 62.

Time to onset (n=110):
Range: 1 – 17 days
Mean: 2 days
Median: 1 day

Types of non-fatal AE reviewed (n = 123):
Hallucination, delirium, delusion: n = 30
Convulsion: n = 25
Depressed level of Consciousness, disorientation, confusional state, encephalopathy, encephalitis: n = 23
Loss of consciousness: n = 17
Abnormal Behavior: n = 15
Anxiety, agitation, excitability, panic reaction, schizophrenia, mania, mental disorder, crying: n = 13

6.3.1 Summary Table of Non-Fatal Neuropsychiatric Events

AE Groups	Fever	Indication use for influenza/ Tested for influenza	Normal EEG/MRI/ CT Scan/ neurological exam	Positive Dechallenge/ Rechallenge	Treated with anticonvulsant/ antipsychotic/ tranquilizer
Hallucination, Delirium, Delusion n = 30 Age : 3 – 87 yrs (n = 28) Mean: 26.6 yrs Median: 9.5 yrs M = 20, F = 9	n = 15 37.3 – 43^{0}C (n = 11)	n = 27 Influenza A = 5 Influenza B = 4	n = 4	Positive dechallenge = 16 Positive rechallenge = 1	n = 3
Convulsion n = 25 Age : 0.8 – 92 yrs Mean: 30.8 yrs Median : 19 yrs M = 11, F = 14	n = 17 37.2 - 40^{0}C (n = 10)	n = 23 Influenza = 3 Influenza A = 4 Influenza B = 6 Influenza Neg = 1	n = 11 Abnormal = 4	Positive dechallenge = 8	n = 10
Depressed Level of Consciousness, Disorientation, Confusion Encephalitis/encephalopathy n = 23 Age : 1 – 94 yrs Mean: 41 yrs Median: 49 yrs M = 9, F = 14	n = 15 37.1 - 40^{0}C (n = 10)	n = 19 Influenza = 2 Influenza A = 6 Influenza B = 1 Influenza AB = 1 Influenza Neg = 2	n = 6 Abnormal = 1	Positive dechallenge = 15 Positive rechallenge = 2	n = 2
Loss of Consciousness n = 17 Age : 3 – 76 yrs Mean: 38.6 yrs Median: 44 M = 9, F = 8	n = 12 35.4 – 39.3^{0}C (n = 11)	n = 17 Influenza A = 2 Influenza B = 7 Influenza Neg = 1	n = 2	Positive dechallenge = 8 Positive rechallenge = 1	n = 4
Abnormal Behavior n = 15 Age : 7 – 90 yrs Mean: 25.3 yrs Median: M = 12, F = 3	n = 12 37 – 39.5^{0}C (n = 9)	n = 15 Influenza = 1 Influenza A = 3 Influenza B = 2	n = 4 Abnormal = 1	Positive dechallenge = 10 Positive rechallenge = 2	n = 1
Agitation, Anxiety, Crying, Mania, Mental Disorder, Panic Attack, Psychotic Syndrome, Schizophrenia, Thinking Abnormal n =13 Age : 1 – 81 yrs Mean: 29.3 yrs Median: 15 M = 6, F = 7	n = 5 38.9 – 40^{0}C (n = 3)	n = 11 Influenza = 1 Influenza A = 2	n = 3	Positive dechallenge = 4	n = 3

6.4.1 Notable Case of Neuropsychiatric Event

AERS Case # 3426683, US: a 45-year-old male patient with no known drug allergies, unremarkable past medical history who does not smoke or drink alcohol experienced delusions, hallucinations, disorientation, confusion and abnormal behavior. The patient presented with fever, chills, body aches, and a cough was prescribed oseltamivir 75 mg twice daily. The patient took one dose in the morning and later that day, he appeared to be confused and disoriented. The patient went outside of his home in his underwear, and he tried to eat his compact disc with salt and pepper. The patient went to the ER where his temperature was recorded to be 98.5^0F. He was administered Tylenol, and oseltamivir was discontinued. The next day, the adverse event resolved.

6.4.2 Notable Cases of Fatal Neuropsychiatric Events

AERS Case # 5787263, Japan: a 14-year-old male patient visited a clinic complaining of fever, arthritic pain, and pharyngeal pain; he tested positive for influenza Type A. No disturbed consciousness or mental symptoms were observed. At 4:00pm the patient took one capsule of Tamiflu. At 6:00pm, the patient was reported to have fallen from the 9^{th} floor of his apartment. The patient died of hemorrhagic shock at the hospital. The physician commented that "the patient took only one capsule of Tamiflu before his death; it is not clear whether the patient was having disturbed consciousness or mental disorders because no one witnessed the circumstances of the fall. It may be safe to say that taking Tamiflu may have been related to the event. Influenza encephalopathy may be possibly other contributing factor."

AERS Case # 4165603, Japan: a 17-year-old male patient experienced abnormal behavior and subsequently died while receiving oseltamivir and amantadine. The patient experienced pyrexia, headache, cough, and nasal discharge in the morning before presenting to the hospital. He had a normal breakfast and a temperature of 38.6^0C. He tested positive for influenza Type A and negative for influenza Type B and C-reactive protein (CRP). The patient was reading while receiving "unspecified drop infusion," he was able to talk to staff as usual with clear consciousness despite his fever. He did not complain of any trouble or worry, and no special pathology was observed except fever upon examination. The patient was instructed to stop amantadine, the last dose was that morning, and to start oseltamivir 75mg after lunch. The patient went to sleep half an hour after taking oseltamivir. Ninety minutes later, the patient ran out of his house without shoes while the snow was falling; he jumped over a one-meter concrete wall, crossed the railroad, over a guard rail of the national highway and leaped into the path of a truck. The patient died at the hospital of shock caused by traumatic injury of the chest. Since this traffic accident was due to the abnormal behavior and the case was considered by the police as a suicide. The reporting physician did not confirmed whether the patient had any other drugs including health foods and herbal medicine; he did not diagnosed encephalopathy because CRP was negative and the patient's response was normal. The reporting physician also assessed the abnormal behavior as related to oseltamivir. No autopsy was performed.

6.4.3 Notable Cases of Non-Fatal Abnormal Behavior Events

AERS Case # 5768481, Japan: an 8-year-old male patient tested positive for influenza and was prescribed oseltamivir 55mg PO BID. He took oseltamivir around 1030h in the morning and went to bed. Immediately after waking up around 1330h, the patient experienced hallucination and exhibited abnormal behavior. He seemed frightened by something and rushed outside. Some of his family members happened to be present at the time and was able to stop him. His mother expressed that "if she had been alone, she would not have been able to stop him rushing to the street, and there could have been an accident." The patient was examined at the clinic again, he received normal saline IV, and the symptoms subsided.

AERS Case # 3922896, Japan: a 13-year-old female diagnosed with influenza started oseltamivir 75mg PO BID in the evening. The next day, "the patient's temperature decreased from 39^0C, at the same time, the patient attempted to run and jump out of a window. The patient was restrained and commenced to utter a strange sound." It was reported that when the body temperature was between 37 and 38^0C, there was no problem taking oseltamivir. The patient continued to utter strange sounds the next three days until the oseltamivir discontinued. The patient was seen at the clinic, she appeared normal, the hallucination was considered resolved.

6.5 Discussion

Norio Sugaya[3] stated that "influenza encephalopathy is typically associated with a sudden onset of high fever, severe convulsion, rapidly progressive coma and death within 2 or 3 days. Very early coma development (mostly within 24 h after the onset of fever) and a high mortality rate are the hallmark of influenza encephalopathy reported in Japan." McCullers et al[4] wrote that "influenza virus can cause a wide spectrum of neurological disease including somnolence, coma, delirium, psychosis, behavioral disturbances, and oculogyric crisis."

In this cases series there were a variety of neuropsychiatric events reported with the use of oseltamivir including three fatalities. Two of these fatalities involved teenagers who exhibited abnormal behavior; 14 and 17-year-old males **(Cases # 5787263, 4165603)** described in the previous section (Section 6.4.2). Both were reported to have no disturbances in consciousness or mental symptoms before receiving oseltamivir, and both patients took only one dose of oseltamivir before their fatal event which occurred two hours and 90 minutes later, respectively. The 14-year-old had no witness to the circumstances of his fall.

The third fatal case involved a 72-year-old male **(Case # 5776474)** with symptoms of fever and cough who tested positive for influenza Type A. The same day, he was given oseltamivir 75mg orally once daily and diclofenac 25mg rectally once a day. The patient's fever abated and three hours later he was found "prostrate with cardio-respiratory arrest" by a nurse. Cardio-pulmonary resuscitations were performed but he did not recover and was confirmed dead. Influenza encephalopathy was suspected. An autopsy on the same day revealed brain edema and bowel necrosis.

[3] Sugaya N. Influenza-associated encephalopathy in Japan: Pathogenesis and treatment. *Pediatrics International* 2000 Apr;42(2):215-8
[4] McCullers JA et al. Influenza B virus encephalitis. *Clin Infect Dis* 1999 Apr ;28(4) :898-900

For the purpose of this review the remaining 123 non-fatal neuropsychiatric adverse event reports were grouped by major adverse events: 1) hallucination, delirium, and delusion (n=30); 2) convulsion (n=25); 3) depressed level of consciousness, disorientation (n=23); 4) loss of consciousness (n=17); 5) abnormal behavior (n=15); 6) agitation, anxiety, crying, mania, mental disorder, panic attack, psychotic syndrome, schizophrenia, and thinking abnormal (n=13). Please note that patients may also experience other neuropsychiatric events concurrently as described in any of the six groups and that many of these neurological symptoms have also been reported in association with the influenza virus[4].

The 15 patients in the "abnormal behavior" group exhibited the most concerning symptoms with their actions resulting in bodily harm in some of the cases. Three out of five Japanese patients ranging in age from 8 – 17 years jumped out of windows in their houses; the 17-year-old male patient **(Case # 4163923)** broke both lower limbs requiring hospitalization. Two younger patients, an 8-year-old male and a 13-year-old female **(Cases # 5768481, 3922896 – Section 6.4.3)** were rescued by their family members from having a tragic outcome. The male seemed to be frightened by something and rushed outside of the house onto the street, and the female attempted to run and jump out of a window. Two 90-year-old female patients **(Cases # 5767687, 4102524)** from Japan and Germany became aggressive; one was violent toward the hospital staff and the later overthrew a table and a TV in her living room. The rest of the patients exhibited dysgraphia, unmeaning speeches, meaningless movement of fingers, threw their clothing and the TV remote control in the trash, and one patient made his wife and children go away for fear he would use "an edged tool." He also kicked down the door of his house.

A disproportionate numbers of the abnormal behavior reports are from Japan; however, we noted one domestic report describing a 45-year-old male patient **(Case # 3426683)** who does not smoke or drink alcohol, had no known drug allergies and an unremarkable past medical history. The patient took one dose of oseltamivir in the morning and later in the day he appeared to be confused, and disoriented commencing to show abnormal behaviors as he went outside of his house in his underwear and tried to eat his compact discs with salt and pepper. After discontinuation of oseltamivir, the patient's abnormal behavior resolved. This US report gave us one good documented sample case to compare with the Japanese patients who experienced similar unexplainable abnormal behavior.

Most patients did not have high fever at the time their neuropsychiatric adverse events developed; some even had decreased body temperature when their symptoms occurred. The US patient had a recorded body temperature of 98.5 ^{0}F at the ER. A few patients, 29% (36/126) reported no abnormal findings with their head CT scan, MRI, EEG or in their cerebrospinal fluid. These patients had one or more tests performed with six reports of an abnormal finding. Among the six patients with abnormal test results, there was one positive dechallenge and one positive rechallenge case. Four patients were treated with anticonvulsants. Unfortunately, there is no information provided of any tests performed for the US case.

6.6 Summary

These cases of neuropsychiatric events are compelling. In particular, the 17 cases of "abnormal behavior" (including two reported deaths) remain a source of concern due to the striking nature of these reports that is uncharacteristic of our usual clinical experience with influenza encephalopathy. At a November 18, 2005, Pediatric Advisory Committee ODS presented an overview of the pediatric abnormal behavior cases and concluded that the US adverse event reports do not show deaths or comparable CNS effects in the pediatric age group as seen in the Japanese data. Based on this current case series we do not have enough domestic cases to make a comparison, establish a clear relationship or

draw a reasonable conclusion to determine whether these neuropsychiatric events warrant inclusion in the oseltamivir label. We are uncertain at this time if there is a possible drug-disease contribution to these reported adverse events.

As oseltamivir is being used globally on a large scale, we may potentially see more reporting from other geographical regions (i.e. US and European) where the data collected from different populations may provide useful information for further analysis. We will continue to closely monitor these neuropsychiatric events and will promptly communicate any new findings to DAVP.

7. SERIOUS SKIN EVENTS

7.1 Relevant Tamiflu® Labeling for Serious Skin Events

The current labeling dated 6/24/2004 contains the following terms related to skin adverse events:

1. ADVERSE REACTIONS, under Treatment Studies in Pediatric Patients section: "Dematitis" is listed in Table 4.
2. ADVERSE REACTIONS: Observed During Clinical Practice for Treatment section, under General: Rash, swelling of the face or tongue, toxic epidermal necrolysis.

7.2 Search results (n = 43)

There were 65 reports of serious skin adverse events associated with the use of Tamiflu® (oseltamivir phosphate) in the FDA Adverse Event Reporting Systems (AERS). All 65 reports were manually reviewed. Fifty-three unduplicated cases were identified.

Three cases were excluded from the review because the reported events of Stevens-Johnson syndrome (SJS), erythema multiforme (EM), and SJS/toxic epidermal necrolysis (TEN) occurred after the discontinuation of oseltamivir therapy (4, 6, and 13 days, respectively). Although Revis DR[5] described that "following the institution of a new drug regimen, the mean time of onset of clinical disease is 9-14 days," the adverse events in these three cases started several days after oseltamivir therapy stopped and started after cephalosporins and macrolides were administered; thus, we have excluded these three cases from further review. We also excluded the seven non-severe cases of blisters and dermatitis.

The remaining **43** unduplicated cases were reviewed for this consult.

7.3 Summary of Data (n = 43)

Demographics:

Age: n = 40
Mean = 29 years
Median = 21.5 years
Range: 3 to 89 years of age
0 – 16 years: n = 16
17 – 89 years: n = 24

Sex: n = 41
Male = 16
Females =25

[5] Revis DR: Erythema Multiforme (Stevens - Johnson syndrome). *eMedicine* June 13, 2005
Author: Don R Revis, Jr. MD, Consulting Staff, Dept of Surgery, Div. of Plastic and Reconstruction Surgery. U of FL College of Medicine

Location: Japan –34, and US – 7, Australia – 1, and France – 1,

Outcomes:
Death – 3, Life-threatening – 6, Hospitalization – 16, Disability – 1, Other/Medically significant – 17.

Types of AE	Time to Onset of AE (days)	Drug discontinued when AE developed	Drug continued when AE developed	Drug discontinued, then AE developed (days)
All Serious Skin (n = 43)	Range: 1 – 8 (n = 42) Mean: 3	**n = 18**	**n = 9**	n = **15**
			2 more days: n = 5 1 more day: n = 4	Range: 1- 3
SJS (n = 24)	Range: 1 – 8 Mean: 3	**n = 12**	**n = 6**	n = **6**
			2 more days: n = 3 1 more day: n = 3	1 day
TEN (n = 4)	Range: 1 – 8 Mean: 5	**n = 1**	**n = 3**	None
			2 more days: n = 2 1 more day: n = 1	
EM (n = 14)	Range: 1 – 8 (n = 13) Mean: 4	**n = 5**	**n = 2**	n = **6**
			2 more days: n = 2	Range: 1- 3
Pemphigus (n = 1)	1 day		**n = 1** 1 more day: n = 1	None

7.4.1 Notable Cases of Serious Skin Event

AERS Case # 3984520, Japan (SJS): a 4-year-old male patient with a negative flu antigen test began oseltamivir 30 mg BID for four days for flu-like symptoms on 2/21/03. On 2/23/03, patient developed SJS; he had rash on his hand and foot, intra oral erosion and erosion of the labia oris. Oseltamivir was discontinued on 2/24/03. The patient was treated with dexchlorpeniramine, flavin adenine dinucleotide, and Vaseline when he visited the clinic on 2/25/04. On 3/1/03, erosion o the end of the penis was observed and 3/3/03, the patient experienced erosion of the anal region and bleeding of the end of the penis, and he was hospitalized on (b) (6). With topical and systemic treatment with steroids and antihistamine, the SJS improved and he was discharged.

AERS Case # 3919655, Japan (SJS): a 54-year-old female patient with high fever, epigastric pain was diagnosed with flu and started oseltamivir 150mg daily for five days. The patient noticed a generalized rash two days after treatment. She went to the hospital and was diagnosed with SJS; generalized rash and conjuntival hyperemia were observed, her mouth was normal, BP: 120/70, pulse: 72. The patient's eruption was described as eczematous, scarlet in color with its size and distribution as 0.5cm – 2cm many with normal skin. The eruption had occurred throughout the whole body and itchy. The eruption had persisted for four days and had become progressively aggravated. After the discontinuation of oseltamivir and treating with steroids, the patient's condition significantly improved without relapse. The reporting physician stated that oseltamivir was the only drug used by the patient, no concomitant medication was administered.

7.4.2 Notable Case of Fatal Serious Skin Event

AERS Case # 5776451 (5799454, 5785913), Japan (TEN): A 58-year-old male who "did not have any medical history and hypersensitivity to oseltamivir" began oseltamivir 150mg once daily, cefdinir TID, and PL (caffeine/paracetamol/promethazine/disalicylate/salicylamide) therapies on 2/23/05 for headache, pharyngeal pain, fatigue, fever, and arthritic pain. Two day later the fever and arthritic pain persisted, and the patient received Fosmicin (fosfomycin sodium) and Primperan (metoclopramide HCL). By this time, actinic erythema on the cervical region was occurring and the patient was admitted to the oto-rhino-laryngology department. The next day the actinic erythemas became generalized, and later became inflamed and blistered. On 2/28/05, the patient was referred to the dermatology department where steroid pulse therapy was given until 3/1/05, and the eruptions did not spread. On 3/2/05, the eruptions were discolorizing. On the afternoon of (b) (6), the patient went into shock due to respiratory failure; endotracheal intubation and artificial respiration were conducted. A hemocatharsis therapy was performed, and albumin preparation Gamma globulin and antibiotic were administered. On (b) (6) the patient did not respond to the therapy and died. Cause of death was toxic epidermal necrolysis, no autopsy was performed.

7.5 Discussion

A review of the postmarketing safety data from the AERS database identified 43 unduplicated cases of serious skin events for further review. The majority of the reports were from Japan (34/43); 7 reports were from the US, then one each from Australia and France. There were 16 pediatric patients from 0 – 16 years of age. Among these 43 cases, there are 24 cases of Stevens-Johnson syndrome (SJS), 14 cases of erythema multiforme (EM), four cases of toxic epidermal necrolysis (TEN), and one case of pemphigus.

The current labeling lists dermatitis under the ADVERSE REACTIONS/Treatment Studies in Pediatric Patients (Table 4) sections and lists rash and toxic epidermal necrolysis under ADVERSE REACTIONS/Observed During Clinical Practice for Treatment/General sections.

For the purpose of this review, we classified the 43 cases as either *probably related* or *possibly related* to the use of oseltamivir. Cases that are classified of "probably related" are defined as those that meet the following criteria 1) a temporal relationship between the occurrence of the adverse event and the use of oseltamivir and 2) the introduction of oseltamivir as the only drug at the time of the event. "Possibly related" cases are defined as having a temporal relationship between the occurrence of the adverse event and the use of oseltamivir but include confounders such as the concurrent use of other medications associated with serious skin reactions.

7.5.1 Fatal Serious Skin Events (n = 3)

There were three fatalities involving all adult patients. A healthy 58-year-old male patient **(Case # 5776451)** died of TEN after receiving oseltamivir. This case is described under section 7.4.2. Klein PA[6] stated that "Toxic epidermal necrolysis (TEN) is an acute dermatologic disease, the presentation of which may constitute a true emergency. This disorder is characterized by widespread erythematous macules and targetoid lesions; full-thickness epidermal necrosis, at least focally; and involvement of

[6] Klein PA: Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. *eMedicine* June 13, 2005
Author: Peter A Klein, MD, Staff Physician, Dept. of Dermatology, Univ. Hospital, State Univ. of NY at Stony Brook

more than 30% of the cutaneous surface. Commonly, the mucous membranes are also involved. Nearly all cases of TEN are induced by medications, and the mortality rate can approach 40%." This patient received a cephalosporin antibiotic, and PL (caffeine/paracetamol/promethazine/disalicylate/salicylamide) concomitantly, but he did not have a hypersensitivity to oseltamivir. The actinic erythema on the cervical region occurred two days after initiation of these medications and the patient's condition worsened rapidly; he did not respond to the intervention treatment and died 11 days after initiation of oseltamivir therapy. The reporting dermatologist assessed the TEN is related to oseltamivir and as the cause of death. The physicians commented that "any of oseltamivir, cefdinir or PL had possible causality to the event; although it can not be determined which one of these had a causal relationship with the event because fever occurred on the second day of administrating these three drug. It is known that each of the drugs can cause TEN for the rare occasion." Nevertheless, this patient died of TEN after receiving oseltamivir that he did not exhibit hypersensitivity prior to the administration.

For the other two fatalities, the serious skin event was probably related to the use of oseltamivir in one and possibly related to the use of oseltamivir in the other; however, cause of death was confounded by other factors. One patient, a 62-year-old female (**Case # 5747260)**, had many underlying chronic diseases including hypertension, diabetes mellitus, and hypothyroidism. Oseltamivir was the only new medication introduced when she developed EM two days later diagnosed by a dermatologist. The reporting physician considered the EM as related to oseltamivir therapy, and believed that the patient had an infection other than influenza which developed into sepsis, and lead to DIC followed by pulmonary embolism and eventually the death of the patient. The outcome for this case was incorrectly coded as "hospitalization" but the narrative reported the patient had died; the sponsor has been requested to submit follow-up information for this case. The last case reported a 65-year-old female **(Case # 3802980)**, with a history of immunoglobulin A nephropathies, who developed pemphigus vulgaris after receiving oseltamivir therapy concomitantly with azithromycin, a macrolide antibiotic, which is labeled for serious skin adverse events. Although, she received azithromycin for a sore throat five months prior without adverse effect; a rechallenge of azithromycin could be a contributing factor, but, the adverse event occurred after oseltamivir was given.

7.5.2 Non-fatal Serious Skin Events (n = 40)

Stevens-Johnson syndrome (n = 24)

Fifteen cases of SJS are considered *probably related* to the use of oseltamivir because oseltamivir was the only medication introduced at the time the adverse event (AE) developed, or the co-suspect medications were given after the oseltamivir therapy and after the AE had occurred. These patients were healthy, had no underlying diseases other than having the flu or flu-like symptoms for which oseltamivir was prescribed. They developed serious skin reactions after administration of oseltamivir. Ten patients did not take any concomitant medications or antipyretic analgesics at the time of the adverse event. Five patients received other concomitant medications such as penicillin, cephalosporin, macrolide antibiotics or anticonvulsants after oseltamivir were introduced.

The second group of nine patients is considered *possibly related* to the use of oseltamivir because at the same time they were also receiving other concomitant medicaitons such as penicillin, cephalosporin, macrolide antibiotics, acetaminophen or non-steroidal anti-inflammatory agents that could be considered confounding factors to the development of SJS. For example a 10-year-old female patient in the second group received two doses of cefcapene and started oseltamivir when a rash was already appeared on her

face. The patient then received two doses of 37.5 mg of oseltamivir that were discontinued in the afternoon. Later in the evening, the patient received IV fosfomycin for fever; the rash on the patient's face blistered. Oseltamivir may be a contributing factor to the worsening of the pre-existing rash in this patient. The symptoms became worse after oseltamivir was started and it was difficult to judge if there was a possibility that oseltamivir was related to the event. Another notable case involved a patient who took one dose of oseltamivir with concomitant allopurinol and Hyzaar. He was diagnosed with SJS by a dermatology biopsy and progressed to TEN six days later with 30% epidermal involvement.

All reported cases of SJS are severe, debilitating and the patients required hospitalization and intervention with systemic/topical steroids, antihistamines, and antibiotics; in addition, one patient was required to be transferred to the burn unit at a large medical center. Some of the reported clinical manifestations included fever, painful mucocutaneous lesions, stomatitis, swelling of epiglottis, conjuntival hyperemia, desquamation, scales, edema, pigmentation, bleeding genitalia, and Nikolsky's sign. All patients presented to the emergency room or ambulatory clinic, and most of them were then hospitalized; the diagnosis of SJS was further confirmed by departments of dermatology, ophthalmology, or internal medicine.

Erythema multiforme (n = 13)
Using the same criteria to assess the causal relationship with oseltamivir in the EM cases as in the SJS cases we identified eight cases of EM that are considered *probably related* to the use of oseltamivir and five cases that are considered *possibly related* to oseltamivir therapy. Six patients were hospitalized and four patients were treated with systemic/topical steroids. All patients' serious skin events improved and resolved after withdrawal of oseltamivir and treatment for the EM skin lesions. All patients were healthy with no previous history except one reported a childhood history of asthma, and all patients were reported to have never had adverse reactions with a similar class of drugs.

Toxic epidermal necrolysis (n = 3)
All three cases are considered *possibly related* to the use of oseltamivir because these patients received other concomitant medications such as ibuprofen[7], diclofenac, metformin, glicazide, all of which have a reported association with serious skin reactions.

Garra GP[8] *et al* stated that "TEN represents the most severe variant of a disease spectrum that consists of bullous erythema multiforme (EM) and Stevens-Johnson syndrome (SJS). Each of the disorders shares common features including widespread distribution of skin lesions, predominantly on the trunk and face with involvement of one or more mucus membranes." Two patients **(Cases # 3807482, 5816241)** experienced life-threatening adverse events and required hospitalization in intensive care units due to development of multiple infections from epithelial loss.

[7] Bygum A et al: Acetaminophen-Induced Toxic epidermal Necrolysis in a Child. *Pediatric Dermatology* 2004 May-Jun;21 (3):236-8
[8] Garra GP, Viccellio P: Toxic Epidermal Necrolysis. *eMedicine* June 13, 2005
Authors: Gregory P Garra, DO, Clinical Asst Prof of Emergency Medicine, Stony Brook U School of Medicine; Program Dir., Dept of EM, Stony Brook U Hospital.
Peter Viccellio, MD, Vice-Chair, Prof., Dept of EM, State U of NY at Stony Brook

7.6 Summary

The majority (56%, 24/43) of the serious skin reactions were classified as having a high probability of being associated with the use of oseltamivir based on the following criteria:

1. There was a temporal relationship between the occurrence of the adverse event and the use of oseltamivir.
2. Oseltamivir was the only drug introduced at the time of the event.
3. Serious skin reactions are typically not associated with influenza disease; and
4. Serious skin reactions are typically associated with drugs.

Many cases also required patients be hospitalized and receive supportive treatment (i.e. steroids, antihistamines) for their serious skin adverse events.

In light of the numerous serious skin cases reported in the post-marketing AERS database and a clear relationship between the reported event and the use of oseltamivir in the majority (56% or 24/43) of the cases, the current labeling should be strengthened with regard to serious skin adverse events by listing these events in a more prominent place in the oseltamivir label.

The following is possible wording for your consideration that we recommend be added to the current labeling under the PRECAUTIONS section:

"Hypersensitivity Reactions: Anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported in post-marketing experience with TAMIFLU. TAMIFLU should be stopped and appropriate treatment instituted if an allergic-like reaction occurs or is suspected."

And, under ADVERSE REACTIONS section, Observed During clinical Practice sub-section, the following paragraph should also be added: "*Dermatologic: dermatitis, eczema, rash, urticaria, Stevens - Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis (see PRECAUTIONS)."*

8. ANAPHYLACTIC/ANAPHYLACTOID REACTIONS

8.1 Relevant Tamiflu® Labeling for Anaphylactic/Anaphylactoid Reactions

Oseltamivir is not currently labeled for anaphylactic/anaphylactoid reactions. However, the current labeling contains the following terms under ADVERSE REACTIONS section/Observed During clinical Practice for Treatment section/ General: Rash and swelling of the face or tongue.

8.2 Search results (n = 75)

There were 115 reports of anaphylactic/anaphylactoid-like reactions associated with the use of oseltamivir in AERS. All 115 reports were manually reviewed, and 106 unduplicated cases were identified of which 31 reports (eight fatal and 23 non-fatal) were excluded from further discussion; see APPENDIX B for a list of reasons for all exclusions.

The remaining **75** unduplicated cases were reviewed for this consult.

8.3 Summary of Data (n = 75)

Demographics:

Age: n = 65
Mean = 37.3 years
Median = 38 years
Range: 0.8 to 85 years of age
0 – 16 years: n = 12
17 – 89 years: n = 53

Sex: n = 70
Male = 31
Females = 39

Location: Japan –42, US – 22, Germany – 6, Canada – 2, Australia – 1, France – 1, and Slovenia – 1

Outcomes:
Hospitalization – 29, Life-threatening – 9, Required Intervention – 1, Other/Medically Significant – 36

Types of non-fatal AE reviewed (n = 75):
Anaphylactic shock – 17
Hypersensitivity – 16
Face edema (6), Swelling face (4) – 10
Angioneurotic edema – 8
Anaphylactoid reaction – 6
Anaphylactic reaction – 6
Drug hypersensitivity – 4
Laryngeal (1), pharyngeal (2) edema – 3
Eyelid edema – 2
Tongue edema – 1
Drug eruption – 1
Immune system disorder – 1

8.4 Notable Cases of Anaphylactic/Anaphylactoid Reactions

AERS Case # 3450922, US: a 59-year-old female patient has no known allergies or medical history, did not smoke or consumed alcohol. She also had not received an influenza vaccination and was not taking any concomitant medication. The patient developed a sore throat and body aches with a fever of 101-103^{o}F. She was given oseltamivir 75 mg PO BID. Approximately one hour after the first dose, the patient's face began to itch and became red. Her eyes became slightly swollen. These symptoms began to subside in between the doses. At approximately 7 pm, the patient took her second dose of oseltamivir and the redness and itchiness that were affecting her face and swollen eyes reappeared and were more severe. Oseltamivir therapy was discontinued. The patient reported that the redness and itching of her face and swollen eyes had resolved the following day.

AERS Case # 3586421, US: a 39-year-old female patient with an unremarkable medical history and no known allergies or concomitant medications started oseltamivir 75mg PO BID for influenza. The patient had not traveled in the recent past and was negative for streptococcus. She had a fever of 101^{0}F. After three day of therapy, the patient's fever rose to 105^{0}F and she developed an allergic reaction and erythema nodosum, intense myalgia, and headache. Rheumatic fever was ruled out and oseltamivir was discontinued because the treating physician no longer considered that the patient had flu. The next day,

the patient developed diffuse, red popular subcutaneous nodules concentrated on her lower extremities and also more diffusely on her arms. The patient was given acetaminophen and ibuprofen for fever of 104^0F. The patient presented to the ER the next day with continuing fever, myalgia, malaise, lower leg edema, and erythema nodosum. A biopsy of one of the nodules was taken which revealed a perivascular vasculitis consistent with a drug reaction. Subsequently, the patient was treated with methylprednisolone injection, her fever was 105^0F, and she refused to be hospitalized. She also complained of right upper quadrant tenderness. Tylenol and Advil were discontinued. SGPT and SGOT were in the high 60's, ALK PHOS 199, serum glucose and WBC were elevated. The patient improved over the next three days with a low grade fever and the erythema nodosum had faded to a hyperpigmentation of her legs.

AERS Case # 5758400, JP: a 40 year-old female patient with a history of asthma, urticaria, and food allergy, and was concomitantly receiving loxoprofen, amoxicillin, and theophyllin for unknown indications. The patient started oseltamivir 75mg PO BID for influenza. Half an hour later, she experienced serious anaphylactic shock. The patient was examined at the clinic and had difficulty breathing and a generalized rash; her face was drained of color, and her blood pressure was below 60. She was treated with IV hydrocortisone sodium succinate, epinephrine, and oxygen inhalation, but the patient's blood pressure did not rise. Hydrocortisone IV was re-administered 20 minutes later and the blood pressure still did not rise. A third dose was given again and the patient was transferred to another hospital where she was admitted for further treatment. At that time, her blood pressure had not increased but was stable. Oseltamivir was discontinued that day. Two days later, the physician at the new hospital reported that the patient's blood pressure had begun to increase gradually. The patient was discharged from the hospital two days later as the anaphylactic shock had improved.

8.5 Discussion

The definitions[9] below allow us to establish the basis for this section of the review:

1. **Anaphylaxis** is an acute, generalized allergic reaction with simultaneous involvement of several organ systems, usually **cardiovascular, respiratory, cutaneous,** and **gastrointestinal.** The reaction is immunologically mediated, and it occurs on exposure to an allergen to which the subject had previously been sensitized.
2. **Anaphylactic shock** refers to **anaphylaxis** in which hypotension, with or without loss of consciousness, occurs.
3. **Anaphylactoid reaction** is a condition in which the symptoms and signs of **anaphylaxis** occur in the absence of an allergen-antibody mechanism. In this case, the endogenous mediators of **anaphylaxis** are released in vivo through a non-immunologic mechanism.

The terms "anaphylaxis" and "anaphylactic reaction" are used interchangeably in the reports reviewed.

Among the 75 cases reviewed, there are 12 cases that are considered *probably* related to the use of oseltamivir. The reported cases are from Japan (5), then US (4), Canada (2) and Germany (1). One Canadian report is a literature report[10] entitled "New Influenza Drugs Zanamivir (Relenza) and Oseltamivir (Tamiflu): Unexpected Serious Reactions." Patients' age ranges from 12 – 62 years (mean:

[9] Abba I. Terr, MD, Medical Immunology - 10th Ed. (2001). Ch. 27. Anaphylaxis & Urticaria
[10] MacDonal Lynn. CMAJ, New influenz drugs zanamivir (Relenza) and oseltamivir (Tamiflu): Unexpected serious reactions. Oct 3 2000;163(7):879-81.

43.3, median: 44) with one pediatric patient. There are seven male and four female patients and one unknown gender.

All patients in this group were considered healthy except for having influenza and were treated with oseltamivir at the time of the reporting. No risk factors such as any underlying chronic diseases or allergies were reported, and the physicians reported that the patients have not taken any concomitant medications during oseltamivir therapy. The time to onset of the anaphylactic and/or anaphylactoid reaction is immediately after the first dose for most cases with reported times from 20 minutes to 1-2 hours after a dose of oseltamivir. A 12-year-old boy experienced an allergic reaction with hives, joint swelling and fever three days after initiation of oseltamivir. The only case from Canada reported a patient of unknown age and gender, treated with oseltamivir for **an indication of influenza prophylaxis**; the patient experienced angioneurotic edema after 10 days of oseltamivir therapy. Three patients were hospitalized, one had a life-threatening outcome, and eight were categorized as Other/Medically significant. Three patients had a positive dechallenge and one had a positive rechallenge. Five patients were treated with epinephrine, steroids, and antihistamines. The notable 59-year-old female patient **(Case # 3450922, US)** described in section 8.4.1 had a positive rechallenge.

The remaining 63 cases are considered *possibly* related to oseltamivir because they are confounded with underlying diseases (i.e., asthma COPD, convulsions), and/or received concomitant antibiotics (i.e., amoxicillin, piperacillin, quinolones, azithromycin) or other medications (i.e., NSAID, carbamazepine, phenytoin). Five Japanese patients reported to have taken all the prescribed medications including oseltamivir, NSAID, cephalosporin, piperacillin, herbal medicine in one dose at the same time; this method of administration of medication makes it difficult to assess the suspect medication that may cause the adverse reaction.

Four female patients **(Cases #5780409, 4105669, 5754723, and 5758400, JP)** ages 5, 12, 38, and 40 years respectively, experienced the adverse event half an hour to one hour after receiving oseltamivir. The two pediatric patients improved when oseltamivir was discontinued and the two adult patients required supportive treatment with steroids and antihistamines.

8.6 Summary

The current labeling includes “rash, swelling of the face or tongue” in the ADVERSE REACTIONS section. However, anaphylaxis, anaphylactic shock and anaphylactic/anaphylactoid reactions have been reported in the literature and in the post-marketing reporting. These adverse events are serious and can be life-threatening resulting in hospitalization for supportive treatment with steroids, antihistamines, and dopamine. Therefore, we recommend anaphylaxis along with serious skin reactions be added to the current labeling under the PRECAUTIONS section (see Conclusions/Labeling Recommendations).

9. CONCLUSIONS/LABELING RECOMMENDATIONS

In summary, for the hepatic toxicity adverse events, it does not appear that there is a sentinel case of severe liver toxicity (i.e. liver failure or fulminant hepatitis) among the 21 cases reviewed that could be solely related to oseltamivir therapy. These cases are confounded by other risk factors and concomitant medications. Therefore, we do not recommend adding hepatic failure or fulminant hepatitis to the oseltamivir label at this time.

The majority of patients with renal toxicity also had confounding variables (i.e. dehydration, concomitant medications) to the development of renal insufficiency besides the use of oseltamivir and a sentinel case of severe renal toxicity (i.e. renal failure) was not identified among the 46 cases reviewed that could be solely related to oseltamivir therapy. Therefore, we do not recommend adding renal impairment or renal failure to the oseltamivir label at this time.

Although, the cases of neuropsychiatric events are very compelling and concerning especially with regard to subset of cases classified as "abnormal behavior" which includes two fatal outcomes in Japanese pediatric patients, we do not have enough domestic cases to make a comparison, establish a clear relationship, or draw a reasonable conclusion to determine whether these neuropsychiatric events warrant inclusion in the oseltamivir label at the present time. However, we will continue to closely monitor these neuropsychiatric events and promptly communicate any new findings to DAVP.

Finally, the current labeling should be strengthened with regard to hypersensitivity reactions that include anaphylaxis and serious skin reactions, and we recommend for your consideration that the following possible wording be added to the PRECAUTIONS section of the oseltamivir label:

"Hypersensitivity Reactions: Anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported in post-marketing experience with TAMIFLU. TAMIFLU should be stopped and appropriate treatment instituted if an allergic-like reaction occurs or is suspected."

And, under ADVERSE REACTIONS section, Observed During clinical Practice sub-section, the following paragraph should also be added: "Dermatologic: dermatitis, eczema, rash, urticaria, Stevens - Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis (see PRECAUTIONS)."

APPENDIX A

Fatal Neuropsychiatric Events

Seventeen reported deaths are excluded for the following reasons:

1. Loss of consciousness, depressed level of consciousness, sudden death (n = 9):
   - A 9-year-old boy **(Case # 4100296)** who experienced depressed level of consciousness due to acute pancreatitis
   - A 20-year-old female patient **(Case # 5781667)** was found in respiratory arrest, sudden death, by her family after receiving two days of oseltamivir; the cause of sudden death can not be confirmed because an autopsy was denied by her family.
   - Six patients ranged 61 – 84 years **(Cases # 3901374, 3421843, 3889811, 39447875765029, and 3454158)** who experienced unconsciousness due to fall, and deterioration of their conditions such as multi-organ failure, respiratory failure, sepsis and hypoglycemia.
   - An 88-year-old female patient **(Case # 3925563)** who experienced decreased in consciousness level due to the possibility that she had taken eight capsules of oseltamivir 75mg in one night.
2. Encepalopathy, disturbance in attention (n = 5):
   - A 2-year-old boy **(Case # 3894346)** reported by the second physician that the cause of death was "suspicion of myocarditis because the patient had consciousness until just before cardio-pulmonary arrest" whereas the first physician who reported "encephalopathy" did not know if decreased consciousness or decreased respiratory rated occurred first because he did not examine the patient.
   - A second patient, 19-year-old female **(Case # 5751256)** who died due to influenza encephalopathy, had no additional information provided in the report.
   - A 24-year-old male **(Case # 4115199)** who experienced cerebral hemorrhages, confirmed by cranial CT scan, when the disturbance in attention occurred.
   - The encephalopathy of a 39-year-old male patient **(Case # 3925896)** could not be substantiated due to the rejection of providing further information by the physician.
   - A 70-year-old female patient **(Case # 3457089)** died of encephalitis while receiving oseltamivir for flu and levofloxacin for bronchitis. The autopsy reported a final diagnosis of encephalitis.
3. Convulsions (n = 3):
   - A 3-year-old boy **(Case # 3417696)** with a fever of 42^0C had convulsions before he was given Tamiflu and amantadine.
   - A 59-year-old male **(Case # 3622477)** smoker with a long-term history of seizures, post CVA/hemiparesis, diabetes, and a double leg amputee could have experienced seizures due to hyperglycemia (glucose 218).
   - An 83-year-old male **(Case # 3609833)** with history of COPD, asthma, and renal colic was taking theophyllin, ciprofloxacin, and then ceftriaxone when the seizure occurred – the concomitant administration of theophyllin and ciprofloxacin can increase CNS stimulation that could precipitate the seizure.

Non-Fatal Neuropsychiatric Events

Thirty-seven reports are excluded for the following reasons:

- Patients have history of psychotic disorders and are currently taking anti-depressants or anti-psychotic agents.(n=7)
- Patients have history of convulsions/uncontrollable convulsions, and are also currently taking anti-convulsants.(n=5)
- Patients had developed concurrent severe medical events during oseltamivir therapy i.e., anxiety due to myocardial infarction, hypertension, and pain from otitis media; depressed level of consciousness due to patient in shock, anaphylaxis, hypoglycemia crisis, and one patient had a fall before oseltamivir administration; somnolence due to hemolytic anemia; restlessness and hallucination due to bleeding from necrotizing esophagitis; confusional state and disorientation due to acute renal failure, cerebral infarction; loss of consciousness during sudden ventricular tachycardia development after a colonoscopy; disorientation and anxiety while hospitalized with tachycardia; and lastly two cases of viral encephalitis diagnosis confirmed with EEG, CT and MRI. (n = 22).
- Patient had delirium when her fever was 105^0F. (n = 1)
- Patient experienced delirium when he took oseltamivir together with his sleeping pill; he did not have any adverse event later when he was administered oseltamivir alone while hospitalized. One patient took oseltamivir for three days; she then developed panic with a fever of 40^0C after she was given multiple antibiotics to treat pneumonia subsequently confirmed by X-ray. (n = 2)

APPENDIX B

Fatal Anaphylaxis/Hypersensitivity Events

Eight reported deaths are excluded for the following reasons:

1. A 35-year-old male patient **(Case # 3427932, US)** suffered a cardiac arrest and died due to meningococcal. He developed thrombocytopenia, purpuric rash and leucopenia during the use of oseltamivir. The autopsy findings were Waterhouse-Friderichsen syndrome.
2. A 58-year-old male patient **(Case # 3432039, Canada)** died from cardiac arrest and pneumonia. An autopsy indicated acute purulent bracheobronchitis, bilateral multifocal bronchopneumonis, pulmonary edema, and ARDS; the patient died from septic shock.
3. An-81-year-old male patient **(Case #3439879, US)** took his second dose of oseltamivir, developed a painful swelling under both ears that extended down the sides of his neck. The paramedics told his wife that he had suffered a mild heart attack based on increased cardiac enzymes. Patient developed rhabdomyolysis and multi-organ failure about six weeks later.
4. A 77-year-old male patient **(Case # 3944787, Japan)** received oseltamivir, felt weak and was unable to move his body the next morning; he was taken to the hospital and treated for pneumonia, he later died of multi-organ failure.
5. A 64-year-old male patient **(Case # 5761191, Japan)** with history of schizophrenia, first degree atrioventricular block, was tested positive for influenza B and treated with oseltamivir. Patient was given his second dose of oseltamivir right after his dinner, which he ate smoothly with helper's assistance. The patient suddenly stopped breathing and did not respond to CPR. "There seemed to be no symptoms such as wheezing, rash, and edema in the paryngopharynx that would indicate a possibility of anaphylaxis." No autopsy was performed.
6. A 4-year-old boy **(Case # 5761225, Japan)**[1] who complained of chest distress two days after receiving oseltamivir for prophylaxis because his brother had influenza. He was taken to the hospital where ECG and echocardiogram showed no abnormalities, and no abnormality was noted in the patient's breathing. Later the same night, the patient fell to the ground, breathing with difficulty and struggling. He was in a state of asystole by the time he arrived to the ER by ambulance. His creatine phosphokinase (CPK) was 147, and myoglobin 1331. The following day, CPK and myoglobin had increased to 14000 and 23000 respectively. The patient had a cardiorespiratory arrest and became brain-dead.A 52-year-old male **(Case # 5769065, Japan)** with history of asthma was diagnosed with influenza A, He had a temperature of 39.5^0C, a slight wheezing sound came from his chest, he had no breathing difficulty. He took all the prescribed medications together including oseltamivir when he returned from work, and while lying down in the bedroom, the patient experienced breathing difficulty. He was in cardiopulmonary arrest when the ambulance arrived, while heading to the hospital CPR was performed, and at the hospital, tracheal intubation, cardiac massage, adrenalin, and atropine sulfate were administered; he patient did not respond and his death was confirmed. The autopsy finding indicated the airway was inflamed and pneumonia was observed.
7. A 20-year-old female patient **(Case # 5781667, Japan)** was prescribed oseltamivir for influenza. Before oseltamivir was prescribed, she was taking OTC, PABRON. She seemed to have taken one capsule each at night and the next day around noon she was found in cardiopulmonary arrest by her family. The family refused autopsy to be performed.

Non-Fatal Anaphylaxis/Hypersensitivity Events

Fourteen reports are excluded for the following reasons:

- Peripheral edema due to an old trauma to the leg, allergy to cornstarch, syncope due to renal failure, the swelling tongue already started before oseltamivir was given, hypersensitivity due to jaundice, eosinophilia started before oseltamivir therapy, sore throat still persisted 20 days after the discontinuation of oseltamivir, patient was extremely allergic to sulfa drugs while oseltamivir was recalled due to possibility of sulfamethoxazole contamination, Patient developed shock only after azithromycin dose where oseltamivir was discontinued three days before the start of azithromycin, patient developed idiopathic thrombocytopenic purpura, face edema due to oliguria, drug hypersensitivity due to acute hepatitis, and patient experienced decreased immune response because he developed flu again after receiving oseltamivir, patient experienced an anaphylactic reaction to whatever drugs he took.

Two cases **(Cases # 4113526, 5780410)** were reviewed in the Pediatric Exclusivity Consult[1].

Seven cases **(Cases # 3573815, 3636686, 3719470, 3772261, 3937055, 5773244, 5784723)** reviewed in section **7. SERIOUS SKIN EVENTS**.

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/s/

Evelyne Edwards
12/19/2005 02:46:13 PM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
12/19/2005 03:16:17 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Internal Consult

Pre-decisional Agency Information

To: Jeff O'Neill
Division of Anti-Viral Products (DAVP)

From: Lynn Panholzer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Date: December 12, 2005
Re: Consult request for Tamiflu (oseltamivir phosphate) Capsules and For Oral Suspension (N21-246/S-017; PI, PPI)

Tamiflu (oseltamivir phosphate) Capsules and For Oral Suspension

NDA 21-246/S-017

Thank you for forwarding this consult to DDMAC. The following comments are based on the proposed product labeling dated April 15, 2005, (PPI) from the Electronic Document Room, and dated November 30, 2005, (PI), submitted via e-mail to DAVP.

Package Insert

- Description of Clinical Studies: Studies in Naturally Occurring Influenza, Prophylaxis of Influenza, *Pediatric Patients*
  ADVERSE REACTIONS, Prophylaxis in Pediatric Patients, paragraph 1
  Table 4, entitled "Most Frequent Adverse Events Occurring in Children Aged 1 to 12 Years in Studies in Naturally Acquired Influenza," Household Prophylaxis Trial

  Do these sections of the draft PI refer to the same study? These 3 sections refer to a study of postexposure prophylaxis in pediatric patients, but there are discrepancies in the presentations.

(b) (4)

Clinical trial descriptions and the data from those trials are often presented in promotional materials directed to health care professionals. The details of those trials as conveyed in the approved product labeling provide context for the appropriate interpretation of the study data. We recommend that the descriptions of this study in the draft PI be evaluated for consistency and clarity so that the study can be adequately communicated in promotional materials.

- (b) (4)
- (b) (4)
- DOSAGE AND ADMINISTRATION, Standard Dosage- Prophylaxis of Influenza, Pediatric Patients

  Table: "Recommended Dose for **at Least** 10 Days" (emphasis added)
  Text: "The recommended oral dose of TAMIFLU oral suspension for pediatric patients 1 year and older following close contact with an infected individual is: . . . Therapy should begin within 2 days of exposure. (b) (4)

(b) (4)

Patient Package Insert

We reviewed the proposed changes to the Patient Package Insert and have no comments.

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/s/

Lynn Panholzer
12/12/2005 01:26:38 PM
DDMAC REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21246/S-017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-246 & 21087 SUPPL # 017 & 030 HFD # 530

Trade Name Tamiflu

Generic Name oseltamivir phosphate

Applicant Name Hoffman-La Roche Inc.

Approval Date, If Known 21-087 (10/27/99) & 21-246 (12/14/00)

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

SE5

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:

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) capsules

NDA# 21-246 Tamiflu (oseltamivir phosphate) oral suspension

NDA#

2. Combination product. **N/A**

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 **X**

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:

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	WV16193	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	WV16193	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"):

WV16193

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	WV16193	!
IND # 53,093	YES ☒	! NO ☐ ! Explain:
Investigation #2		!
IND #	YES ☐	! NO ☐ ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? **N/A**

Investigation #1	!

YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Jeff D. O'Neill
Title: Regulatory Health Project Manager
Date: 12/16/05

Name of Office/Division Director signing form: Jeff Murray, MD
Title: Deputy Director, Division of Antiviral Products

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

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/s/

Jeffrey Murray

12/23/2005 09:26:52 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA#: 21-246 Supplement Type (e.g. SE5): SE5 Supplement Number: 017
NDA#: 21-087 Supplement Type (e.g. SE5): SE5 Supplement Number: 030

Stamp Date: 08/18/05 Action Date: 12/21/05

HFD-530 Trade and generic names/dosage form: Tamiflu (oseltamivir phosphate)

Applicant: Hoffman-La Roche, Inc. Therapeutic Class: Antiviral

Indication(s) previously approved: Treatment of influenza patients 1+ years of age, prophylaxis of influenza in patients 13+ years of age.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): One

Indication #1: Tamiflu is indicated for prophylaxis of influenza in patients 1-12 years of age.

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- ☒ **No: Please check all that apply: X Partial Waiver X Deferred X Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min kg mo. yr. 0 Tanner Stage
Max kg mo. yr. <1 Tanner Stage

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._1__ Tanner Stage_____
Max_____ kg_____ mo._____ yr._12__ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- **X Other: Applicant asked to study safety of seasonal prophylaxis.**

Date studies (proposal or request for a waiver for pediatric studies) are due (mm/dd/yy):

Phase 4 commitment due 07/08

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._1__ Tanner Stage_____
Max_____ kg_____ mo._____ yr._12__ Tanner Stage_____

Comments: Current submission evaluated post-exposure prophylaxis in patients 1-12 years of age.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Health Project Manager

cc: NDA
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Jeff ONeill

12/21/2005 02:27:43 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-246 (oral suspension) NDA 21-087 (capsules)	Efficacy Supplement Type SE-5 Efficacy Supplement Type SE-5	Supplement Number 017 Supplement Number 030	
Drug: Tamiflu® (oseltamivir phosphate)		Applicant: Hoffman-La Roche	
RPM: Jeff D. O'Neill		DAVP	Phone # 301-796-0777

Application Type: **(X)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**(X)** Standard **( )** Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	**February 18, 2006**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number **3006005**
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) **N/A**
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify) **N/A**

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	**( )** Yes **(X)** No
• This application is on the AIP	**( )** Yes **(X)** No
• Exception for review (Center Director's memo)	**N/A**
• OC clearance for approval	**N/A**
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(X)** Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**(X)** Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) **N/A** **( )** Verified 21 CFR 314.50(i)(1) **( )** (ii) **( )** (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	**N/A**
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	• **Completed** • **N/A**
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	**( )** Yes, Application #_____ **()** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	**(X)** AP **( )** TA **( )** AE **( )** NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter **( )** Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**( )** Yes **(X)** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**( )** None **(X)** Press Release **( )** Talk Paper **( )** Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**N/A**
• Most recent applicant-proposed labeling	**12/16/05**
• Original applicant-proposed labeling	**04/15/05**

• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**ODS/DDRE – 12/19/05** **DDMAC – 12/12/05**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	**N/A**
• Applicant proposed	**N/A**
• Reviews	**N/A**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**12/12/05 Labeling/PMC Fax**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**12/16/05**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**12/12/05 Labeling/PMC Fax**
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**N/A**
• Pre-NDA meeting (indicate date)	**N/A**
• Pre-Approval Safety Conference (indicate date; approvals only)	**N/A**
• Other	**N/A**
❖ Advisory Committee Meeting	
• Date of Meeting	**N/A**
• 48-hour alert	**N/A**
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	**N/A**
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Medical Team Leader - **12/21/05**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	**12/21/05**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**12/21/05**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**6/10/05**
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	**N/A**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**12/20/05**
❖ Demographic Worksheet *(NME approvals only)*	**N/A**
❖ Statistical review(s) *(indicate date for each review)*	**12/30/05**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**N/A**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**N/A**
• Bioequivalence studies	**N/A**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**12/16/05**

❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**N/A**
• Review & FONSI *(indicate date of review)*	**N/A**
• Review & Environmental Impact Statement *(indicate date of each review)*	**N/A**
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**N/A**
❖ Facilities inspection (provide EER report)	Date completed: **N/A** **( )** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **N/A** **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**12/20/05**
❖ Nonclinical inspection review summary	**N/A**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**N/A**
❖ CAC/ECAC report	**N/A**

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/s/

Jeff ONeill

12/30/2005 10:48:05 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 12, 2005

To: Karen Noh Sr. Program Manager Drug Regulatory Affairs	**From:** Jeff D. O'Neill, ACRN Regulatory Health Project Manager
Company: Hoffmann - La Roche, Inc.	Division of Antiviral Drug Products
Fax number: 973-562-3700	**Fax number: 301-796-9833**
Phone number: 973-562-3812	**Phone number: 301-796-0777**

Subject: Comments for NDA 21-246/S-017

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES X NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 13, 2005

To: Karen Noh, Senior Program Manager, Drug Regulatory Affairs

Address: Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

From: Jeff D. O'Neill, ACRN, Regulatory Health Project Manager, DAVP

Through: Linda Lewis, MD, Medical Officer, DAVP

Concurrence: Katherine Laessig, MD, Medical Officer Team Leader, DAVP

NDA: 21-246/S-017

Subject: Comments regarding NDA 21-246, supplement 017.

We have completed our review of NDA 21-246, SE5-017 and have reviewed your recent responses to labeling comments. This communication contains additional comments on proposed Tamiflu labeling.

Comments regarding the Package Insert:

1. In Table 3, we agree with the numbers of adverse events added in the Prophylaxis columns (b) (4) We believe these should include 1688 and 1790 subjects, respectively. Please include "No Prophylaxis" in the appropriate heading for column 4. In both Tables 3 and 4, please round percentages to the nearest whole number.

2. Please move the paragraph "Prophylaxis Studies in Adult Patients" ahead of Table 3 in the label. In this section, we do not agree with the total numbers of subjects you cite. By my calculations, a total of 4182 subjects ≥ 13 years of age participated (3434 from previous studies + 748 subjects from Study WV16193) and 1790 received Tamiflu prophylaxis. Please clarify your totals.

3. In the safety section Prophylaxis for Pediatric Patients, please delete the phrase, (b) (4) This qualitative statement is considered promotional and vague.

4. After re-evaluating the text and tables in the label, we believe that Table 4 will provide more useful information for practitioners if the column [redacted] is deleted and replaced with a column showing the AEs in those patients randomized to no prophylaxis who never received Tamiflu. This would make the table more analogous to Table 3 and would provide a useful comparison between uninfected pediatric patients receiving and not receiving Tamiflu. Footnote b should be corrected to correlate with the change in displayed data (eg. a randomized, open-label, study of household transmission in which household contacts received either prophylaxis or no prophylaxis but treatment if they became ill). The footnote should explain that only those contacts who received prophylaxis or who remained on no prophylaxis are displayed in the table. These changes will necessitate removing the study treatment dose from footnote c. [redacted]

5. In reviewing the safety data submitted and preparing for the recent Pediatric Advisory Committee meeting, we have consulted with the Office of Drug Safety, Division of Drug Risk Evaluation. They have completed an independent review of post-marketing safety reports submitted to the FDA AERS database. It is our conclusion that serious skin/hypersensitivity reactions have been associated with Tamiflu use, without other likely explanations in some cases. We believe that new language regarding these events should be included in the PRECAUTIONS section as follows:

> Serious skin/Hypersensitivity Reactions: Anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme have been reported in post-marketing experience with Tamiflu. Tamiflu should be stopped and appropriate treatment instituted if an allergic-like reaction occurs or is suspected.

6. In the section, "Observed During Clinical Practice [redacted]," please delete the phrase [redacted] in the heading since [redacted] Under the listing "Dermatologic," please delete the phrase [redacted] and include the listed conditions and a reference to "(see PRECAUTIONS)".

7. In the Dosage and Administration section, the pediatric prophylaxis dose should be described as follows (lines 489-90), "Prophylaxis in pediatric patients following close contact with an infected individual is recommended for 10 days. Prophylaxis in patients 1 to 12 years of age has not been evaluated for longer than 10 days duration. Therapy should begin within 2 days of exposure. Please delete the sentence, [redacted] Also, please delete the words [redacted] from the pediatric dosing table for prophylaxis (column 3).

8. Review of the proposed label has generated some concern that there are inconsistencies between the descriptions of Study WV16193 in the Description of Clinical Studies, Prophylaxis of Influenza section, in the Adverse Reactions section, and in Table 4 and that people unfamiliar with the study might not realize that these sections refer to the same study. Please include in the Description of Clinical Studies section for WV16193 the information that the study was

randomized and open-label and that all index cases received treatment. Also, please clarify that the doses for pediatric patients 1 to 12 years of age were 30 mg to 60 mg as stated in the footnote for Table 4 (not 75 mg).

9. [redacted] (b) (4)

Comments regarding the Patient Package Insert:

1. In the section "How Should I take Tamiflu," please include a statement that Tamiflu has not been evaluated in pediatric patients for prophylaxis longer than 10 days and/or has not been studied pediatric patients for prevention during community outbreaks of flu.

2. Please include a section in the PPI that describes the occurrence of serious skin and hypersensitivity reactions. Patients should be instructed to stop taking Tamiflu and contact their health care provider if they develop a severe rash.

Proposed Phase 4 Commitment:

Collect and submit safety data in a population of 40-50 pediatric patients 1 to 12 years of age using the approved prophylaxis dosing recommendations for a period of up to 6 weeks in the setting of seasonal influenza prophylaxis. Evaluation of "influenza high risk" patient groups is suggested.
Submit protocol by December 1, 2006
Submit final study report by July 1, 2008

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

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/s/

Jeff ONeill
12/13/2005 11:30:33 AM
CSO

NDA 21246/S-017 Labeling comments and PMC proposal. Hard copy sign-off 12/13/05

Kathrine Laessig
12/13/2005 01:32:57 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: DDMAC/Attn. Lynn Panholzer

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Division of Antiviral Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/06/05		21-246/S-017	PI and PPI	04/15/05 and 11/30/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tamiflu	Due to the great interest in pandemic influenza and Tamiflu, management has requested it be completed ASAP.		As soon as possible, but by 12/16/05.

NAME OF FIRM: Hoffman-La Roche

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This supplement extends the prophylaxis indication 6to 1-12 year olds. This drug is already indicated for treatment in this age group.

SIGNATURE OF REQUESTOR
Jeff D. O'Neill

METHOD OF DELIVERY (Check one)
☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Jeff ONeill

12/6/2005 09:38:10 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 17, 2005

To: Karen Noh **Sr. Program Manager** **Drug Regulatory Affairs**	**From: Jeff D. O'Neill, ACRN** **Regulatory Health Project Manager**
Company: Hoffmann - La Roche, Inc.	**Division of Antiviral Drug Products**
Fax number: 973-562-3700	**Fax number: 301-796-9833**
Phone number: 973-562-3812	**Phone number: 301-796-0777**

Subject: Comments for NDA 21-246/S-017

Total no. of pages including cover: **7**

Comments:

Document to be mailed: ☐ **YES** **X NO**

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **November 17, 2005**

To: **Duane Voss, Program Director, Drug Regulatory Affairs**

Address: **Hoffmann-La Roche Inc.**
340 Kingsland Street
Nutley, New Jersey 07110-1199

From: **Jeff D. O'Neill, ACRN, Regulatory Health Project Manager, DAVP**

Through: **Linda Lewis, MD, Medical Officer, DAVP**
Tom Hammerstrom, Ph.D., Statistician, DBIV

Concurrence: **Katherine Laessig, MD, Medical Officer Team Leader, DAVP**
Fraser Smith, PhD, Acting Statistics Team Leader, DBIV

NDA: **21-246/S-017**

Subject: **Comments regarding NDA 21-246, supplement 017.**

The comments are on behalf of Linda L. Lewis, MD, and Tom Hammerstrom, PhD:

We are in the process of completing our review of your efficacy supplement number 017 for NDA 21-246, dated April 15, 2005. This supplement contains the final study report and electronic datasets for Study WV16193, a household prophylaxis study of Tamiflu in patients and contacts > 1 year of age. In addition, an amendment to the sNDA containing a requested post-marketing safety update, dated June 10, 2005, is still under review.

At this time we have the following suggestions to your most recent proposed labeling revisions contained in the June 10, 2005, amendment for this supplement:

1. In the new Prophylaxis of Influenza, Pediatric Patients section, line 223 (Track Changes format Word document), please include that the primary efficacy endpoint was "the incidence of laboratory-confirmed clinical influenza in the household."

2. In line 228, please revise this sentence: "Among household contacts 1 to 12 years of age not already shedding virus at baseline, Tamiflu oral suspension 30 mg to 75 mg taken once daily for 10 days reduced the incidence of laboratory-confirmed clinical influenza from X% (N) in the group not receiving prophylaxis to Y% (N) in the group receiving prophylaxis."

3. In the current proposal for displaying efficacy you are using the population of contacts who acquired laboratory confirmed clinical influenza during the study period, had an index case with documented infection (ITTI), and were not shedding virus at baseline (NAB). Our efficacy analysis reached very similar conclusions but could not confirm the exact proportions infected in the 2 treatment groups. Attached you will find a listing of the contacts (1-12 years) that we have identified as having laboratory confirmed clinical influenza for different efficacy populations (ITT, ITTI, NAB, and ITTINAB). Consider using as the efficacy population for the label the population of contacts who had confirmed flu and NAB. Use of this population will include the potential benefit of short-term prophylaxis against community acquired flu.

4. Please delete the paragraph referring to [redacted] (b) (4) This study does not rise to the level of evidence that is displayed in product labels.

5. Please include patients ≥ 13 years of age enrolled in study WV16193 in Table 3 that displays Most Frequent Adverse Events. The randomized contacts in this study (prophylaxis vs. no prophylaxis) can be combined with those from the previously reviewed prophylaxis studies (prophylaxis vs. placebo).

6. In Table 4, the footnotes describing Study WV16193 are not clear. Please describe the study more fully: for example, a randomized, open-label study of household transmission in which some pediatric patients received prophylaxis and others received treatment for influenza. Also provide the dosing actually used in the study. Pediatric dosing in the U.S. is weight-based, not age-based, so reference to the Dosage and Administration section will not provide the dosing used in the study. There may need to be slightly different headings for the Table so that it is clear that the last 2 columns represent different groups in the same study. See example:

Adverse Event	Treatment Trials		Household Prophylaxis Trial	
	Placebo (N=517)	Oseltamivir 2 mg/kg BID (N=515)	Treatment with Oseltamivir BID (N=158)	Prophylaxis with Oseltamivir QD (N=99)
Vomiting				
Diarrhea				

7. After Table 4 there is a statement regarding what adverse events area included. Please clarify what this refers to.

[redacted] (b) (4)

9. In the section Standard Dosage – Prophylaxis of Influenza, Pediatric Patients, please delete the sentence, "The recommended dose for prophylaxis during a community outbreak of influenza is 75 mg once daily (b) (4)

10. The two pages attached at the top of this fax contain a listing of the different efficacy groups. While the proportions are close, our results do not match the numbers in your supplement, please provide and explination for this difference.

Further labeling comments may be forwarded at a later time as we complete our review.

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

Attachment: 2 pages

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

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

/s/

Jeff ONeill
11/18/2005 08:59:20 AM
CSO

Comments regarding NDA 21-246 supplement 017 Stats and Clin.
Hard copy sign off 11/17/05

Kathrine Laessig
11/21/2005 04:38:03 PM
MEDICAL OFFICER

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS (Room 15B-08, PKLN Bldg.)

FROM: Kenny Shade

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 25, 2005		21,246/S-017	Supplemental NDA	April 15, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tamiflu® (oseltamivir phosphate)	High	7030120	September 23, 2005

NAME OF FIRM: Hoffman-La Roche

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please conduct a review of serious skin/soft tissue disorders, renal toxicity, hepatic toxicity, and central nervous system/psychiatric disorders associated with the use of Tamiflu. The sponsor has provided a safety update on these events, cumulative since approval of Tamiflu, as an amendment to the supplement. (This amendment has already been forwarded to ODS electronically).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kenny Shade	☑MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Kenny Shade

8/25/2005 02:20:41 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 18, 2005

To: Lyn Devenezia-Tobias, Program Manager	**From: Kenny Shade, JD, BSN** Division of Antiviral Drug Products
Company: Hoffman-La Roche	**Title: Regulatory Project Manager**
Fax number: 973-562-3700	**Fax number: 301-827-2471**
Phone number: 973-562-5539	**Phone number: 301-827-2335**

Subject: **Clinical Comments**

Total number of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Date: **August 18, 2005**

NDA: **21-246/S-017**

Drug: **Tamiflu® (oseltamivir phosphate) oral suspension**

To: **Lynn Devenezia-Tobias, Program Manager**

Sponsor: **Hoffman-La Roche**

From: **Kenny Shade, JD, BSN**

Through: **Linda Lewis, M.D.**

Concurrence: **Katherine Laessig, M.D.**

Subject: **Clinical Comments**

The following comments are being conveyed to you on behalf of the review team. Please refer to your NDA 21-246, S-017 for Tamiflu® oral suspension. These comments refer to the dataset submitted for Study WV16193.

1. In the file DEMO, please explain the difference between the variables TRT1GRP, RNDGRP, and TRTGRP2 and which analyses were based on which of these designations.

2. The file DEMO contains data for 1110 study subjects while the study report indicates the disposition of only 1104 subjects in Figure 1, p 44, Clinical Study Report WV16193. Please explain the status of the remaining 6 subjects, which subjects they are, and why their disposition is not included in the study report.

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 301-827-2335 if you have any questions regarding the contents of this transmission.

Kenny Shade, JD, BSN
Regulatory Project Manager
Division of Antiviral Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

Kenny Shade
8/18/2005 02:08:22 PM
CSO

Kathrine Laessig
8/22/2005 02:49:13 PM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 11, 2005

To: Lynn Devenezia-Tobias, Program Manager	**From: Kenny Shade, JD, BSN** Division of Antiviral Drug Products
Company: Hoffman-La Roche	**Title: Regulatory Project Manager**
Fax number: 973-562-3700	**Fax number: 301-827-2471**
Phone number: 973-562-5539	**Phone number: 301-827-2335**

Subject: **Biometrics Request**

Total number of pages including cover: 23

Comments:

Document to be mailed: " YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Date: **August 11, 2005**

NDA: **21-246/SN 017**

Drug: **Tamiflu®(oseltamivir phoshphate) oral suspension**

To: **Lynn Devenezia-Tobias, Program Manager**

Sponsor: **Hoffman-La Roche**

From: **Kenny Shade, JD, BSN**

Through: **Thomas Hammerstrom, Ph.D.**
Linda Lewis, M.D.

Concurrence: **Katherine Laessig, M.D.**
Guoxing Soon, Ph.D.

Subject: **Biometric Request**

The following comments are being conveyed to you on behalf of the review team. Please refer to your NDA 21-246/SN017 submitted April 15, 2005 for Tamiflu® (oseltamivir phosphate) oral suspension.

Please explain why, according to EFEX2A, the following contact subjects have an onset of flu, marked by ONSET1 in the dataset DEMO, when they do not have cough or nasal congestion and fever within a two diary card window of ONSET1. In fact, none of these cases ever have flu.
470 730 816 817 1727 2087 2088 2425 2432 2515 4318 5128 5729 5766 6263 6269 6582 6878 7016 7017

Please explain why the following contact subjects have both temperature>=38 and either cough or nasal congestion within a two diary card window prior to the date ONSET1.
PT = 471 577 1125 1641 2165 2214 2436 2615 4725 4736 4740 4872 4874 5763 6276 6552 6573 6578 6584 6600 6610 6611 6814 6885

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THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.
Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

Kenny Shade, JD, BSN
Regulatory Project Manager
Division of Antiviral Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

Kenny Shade
8/11/2005 09:59:31 AM
CSO

Kathrine Laessig
8/16/2005 10:16:27 AM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 2, 2005

To: Duane Voss	**From: Kenny Shade, JD, BSN** Division of Antiviral Drug Products
Company: Hoffman-La Roche	**Title: Regulatory Project Manager**
Fax number: 973-562-3700	**Fax number: 301-827-2471**
Phone number: 973-562-3519	**Phone number: 301-827-2335**

Subject: Reviewer comments to NDA 21-246/SN017

Total number of pages including cover:10

Comments:

Biometric Comments

Document to be mailed: " YES ☑ NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

Date: **August 2, 2005**

NDA: **21-246/SN017**

Drug: **Tamiflu® (oseltamivir phosphate)**

To: **Duane Voss**

Sponsor: **Hoffman-La Roche**

From: **Kenny Shade, JD, BSN**

Through: **Linda Lewis, M.D.**
Thomas Hammerstrom, Ph.D.

Concurrence: **Katherine Laessig, M.D.**
Guoxing Soon, Ph.D.

Subject: **Biometric Comments**

The following comments are being conveyed to you on behalf of the review team. Please refer to your NDA 21-246/SN017 submitted on April 15, 2005.

1. Please explain why in the dataset DEMO there are 345 contacts who begin treatment earlier than their index cases. Specifically, all of the following, where IPT = PT of the index, CPT = PT of the contact, ITRTDT = DATEPART(TRT1DT) of the index, CTRTDT = DATEPART(TRT1DT) of the contact

(b) (4)

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/s/

Kenny Shade
8/3/05 02:21:15 PM
CSO

Linda this is the biometric fax you signed in
Katie's absence

Linda Lewis
8/3/05 02:29:10 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-246/S-017 **FILING COMMUNICATION**

Hoffman-La Roche
Attention: Lynn DeVenezia-Tobias
Program Manager, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. DeVenezia-Tobias,

Please refer to your April 15, 2005 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tamiflu ®(oseltamivir phosphate) Oral Suspension.

We completed our filing review and determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on June 14, 2005 in accordance with 21 CFR 314.101(a).

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

Additionally, you requested a priority review for this application. After reviewing your rationale for the request, we concluded that this application will be reviewed on a standard review timeline (ten months).

If you have any questions, please call Destry Sillivan Regulatory Project Manager, at (301) 827-2376.

Sincerely,

{See appended electronic signature page}

Virginia Behr
Chief, Project Management
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Virginia Behr

6/21/05 05:43:29 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-246/S-017

PRIOR APPROVAL SUPPLEMENT

Hoffman-La Roche
Attention: Lynn DeVenezia-Tobias
Program Manager, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. DeVenezia-Tobias,

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

Name of Drug Product:	Tamiflu ®(oseltamivir phosphate) Oral Suspension
NDA Number:	21-246
Supplement number:	017
Date of supplement:	April 15, 2005
Date of receipt:	April 18, 2005

This supplemental application proposes the following changes: A provision for an extension of the prophylaxis indication to patients between 1-12 years of age.

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 June 17, 2005 in accordance with 21 CFR 314.101(a).

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room
9201 Corporate BLVD
Rockville, Maryland 20850

If you have any question, please call Destry Sillivan, Regulatory Project Manager, at (301) 827-2376.

Sincerely,

{See appended electronic signature page}

Anthony DeCicco, R.Ph.
Chief, Project Management
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Tony DeCicco

6/6/05 02:36:55 PM