

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

*APPLICATION NUMBER:*

**NDA 021087/S-040**

*Trade Name:* **TAMIFLU**

*Generic Name:* **Oseltamivir Phosphate**

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

*Approval Date:* 07/02/2007

*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

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 021087/S-040**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 021087/S-040**

**APPROVAL LETTER**



NDA 21-087/S-040

NDA 21-246/S-027

Hoffman-La Roche Inc.  
Attn: Ellen Carey, Senior Program Manager  
Drug Regulatory Affairs  
340 Kingsland Street  
Nutley, New Jersey 07110

Dear Ms. Carey:

Please refer to your supplemental new drug applications dated March 8, 2007, received March 9, 2007, 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 dated April 2, 2007, June 4, 2007, June 21, 2007, and June 29, 2007.

Specifically, these supplemental new drug applications provide for:

- manufacture, packaging and testing of the 30 mg and 45 mg capsules at the sites listed in the supplemental application;
- addition of the 30 mg and 45 mg capsules to the **DESCRIPTION** section of the package insert;
- updates to tables 5 and 6 in the **DOSAGE and ADMINISTRATION** section of the package insert to include dosing instructions for the 30 mg and 45 mg capsules;
- addition of descriptions of the 30 mg and 45 mg capsules in the **HOW SUPPLIED** section of the package insert; and
- carton and container labeling for 30 mg and 45 mg foil trade packages, Department of Defense stockpiles, state stockpiles, and Strategic National Stockpiles.

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

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 supplement NDA 21-087/S-040 and NDA 21-246/S-027.**" Approval of these submissions by FDA is not required before the labeling is used.

NDA 21-087/S-040

NDA 21-246/S-027

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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  
5515 Security Lane  
HFD-001, Suite 5100  
Rockville, MD 20852

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  
Center for Drug Evaluation and Research

Enclosures: Package Insert, Patient Package Insert, and Carton and Container Labels

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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.**  
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/s/

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Debra Birnkrant  
7/2/2007 03:58:54 PM  
NDA 21-246, 21-087,

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021087/S-040**

**LABELING**



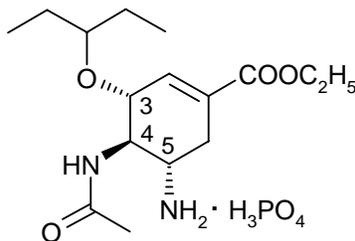
**TAMIFLU®(oseltamivir phosphate)**  
**CAPSULES**  
**AND FOR ORAL SUSPENSION**

**R<sub>x</sub> only**

**DESCRIPTION**

TAMIFLU (oseltamivir phosphate) is available as capsules containing 30 mg, 45 mg, or 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension, which when constituted with water as directed contains 12 mg/mL oseltamivir base. In addition to the active ingredient, each capsule contains pregelatinized starch, talc, povidone K 30, croscarmellose sodium, and sodium stearyl fumarate. The 30 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide, and red iron oxide. The 45 mg capsule shell contains gelatin, titanium dioxide, and black iron oxide. The 75 mg capsule shell contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide. Each capsule is printed with blue ink, which includes FD&C Blue No. 2 as the colorant. In addition to the active ingredient, the powder for oral suspension contains sorbitol, monosodium citrate, xanthan gum, titanium dioxide, tutti-frutti flavoring, sodium benzoate, and saccharin sodium.

Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-5-amino-3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is C<sub>16</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> (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<sub>50</sub> and IC<sub>90</sub>) 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 <sub>max</sub> (ng/mL)	65.2 (26)	348 (18)
AUC <sub>0-12h</sub> (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<sub>ss</sub>) 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 30 mg weekly	Hemodialysis 30 mg alternate HD cycle	75 mg daily	75 mg alternate days	30 mg daily
C <sub>max</sub>	259*	348*	705*	766	850	1638	1175	655
C <sub>min</sub>	39*	138*	288*	62	48	864	209	346
AUC <sub>48</sub>	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 and Prevention Advisory Committee on Immunization Practices.

### ***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  $>100^{\circ}\text{F}$ , accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache) and influenza virus was known to be circulating in the community. In addition, all 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  $\geq 65$  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  $>97.5^{\circ}\text{F}$ . 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 (>100°F) 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  $\geq 99.0^{\circ}\text{F}/37.2^{\circ}\text{C}$  plus at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one constitutional symptom (aches and pain, fatigue, headache, chills/sweats), all recorded within 24 hours, plus either a positive virus isolation or a 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  $\geq 13$  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  $\geq 100^{\circ}\text{F}/37.8^{\circ}\text{C}$  plus cough and/or coryza recorded within 48 hours, plus either a positive virus isolation or a 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 for Oral Suspension 30 mg to 60 mg taken once daily for 10 days reduced the incidence of laboratory-confirmed clinical influenza from 17% (18/106) in the group not receiving prophylaxis to 3% (3/95) in the group receiving prophylaxis.

### **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.

### ***Neuropsychiatric Events***

There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period.

### ***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***

The concurrent use of TAMIFLU with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of the potential for interference between these products, LAIV should not be administered within 2 weeks before or 48 hours after administration of TAMIFLU, unless medically indicated. The concern about possible interference arises from the potential for antiviral drugs to inhibit replication of live vaccine virus. Trivalent inactivated influenza vaccine can be administered at any time relative to use of TAMIFLU.

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 ( $AUC_{0-24h}$ ) 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  $\geq 1\%$  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**

Adverse Event	Treatment				Prophylaxis			
	Placebo N=716		Oseltamivir 75 mg bid N=724		Placebo/ No Prophylaxis <sup>a</sup> 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%)

<sup>a</sup> 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  $\geq 1\%$  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 for Oral Suspension.

Adverse events occurring in  $\geq 1\%$  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**

Adverse Event	Treatment Trials <sup>a</sup>		Household Prophylaxis Trial <sup>b</sup>	
	Placebo N=517	Oseltamivir 2 mg/kg bid N=515	No Prophylaxis <sup>c</sup> N=87	Prophylaxis with Oseltamivir QD <sup>c</sup> 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%)	-	-

<sup>a</sup> Pooled data from Phase III trials of TAMIFLU treatment of naturally acquired influenza.

<sup>b</sup> 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.

<sup>c</sup> Unit dose = age-based dosing

Age	Prophylaxis (10 days)
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  $\geq 1\%$  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 for pediatric patients 1 year and older is shown in **Table 5**. TAMIFLU for Oral Suspension may also be used by patients who cannot swallow a capsule. For pediatric patients who cannot swallow capsules, TAMIFLU for Oral Suspension is the preferred formulation. If the for Oral Suspension product is not available, TAMIFLU Capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup.

**Table 5 Oral Dose of TAMIFLU for Treatment of Influenza in Pediatric Patients by Weight**

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

An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser provided is lost or damaged, another dosing syringe or other device may be used to deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for >15 to 23 kg, 5.0 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 for pediatric patients 1 year and older following close contact with an infected individual is shown in **Table 6**. TAMIFLU for Oral Suspension may also be used by patients who cannot swallow a capsule. For pediatric patients who cannot swallow capsules, TAMIFLU for Oral Suspension is the preferred formulation. If the for Oral Suspension product is not available, TAMIFLU Capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup.

**Table 6 Oral Dose of TAMIFLU for Prophylaxis of Influenza in Pediatric Patients by Weight**

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

An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser provided is lost or damaged, another dosing syringe or other device may be used to deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for >15 to 23 kg, 5.0 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 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 for Oral Suspension***

It is recommended that TAMIFLU for 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 FOR ORAL SUSPENSION WELL BEFORE EACH USE.

The constituted TAMIFLU for Oral Suspension (12 mg/mL) 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.

### **Emergency Compounding of an Oral Suspension from TAMIFLU Capsules** ***(Final Concentration 15 mg/mL)***

The following directions are provided for use only during emergency situations. These directions are not intended to be used if the FDA-approved, commercially manufactured TAMIFLU for Oral Suspension is readily available from wholesalers or the manufacturer.

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

Commercially manufactured TAMIFLU for Oral Suspension (12 mg/mL) is the preferred product for pediatric and adult patients who have difficulty swallowing capsules or where lower doses are needed. In the event that TAMIFLU for Oral Suspension is not available, the pharmacist may compound a

suspension (15 mg/mL) from TAMIFLU (oseltamivir phosphate) Capsules 75 mg using either of two vehicles: Cherry Syrup (Humco®) or Ora-Sweet® SF (sugar-free) (Paddock Laboratories). Other vehicles have not been studied. **This compounded suspension should not be used for convenience or when the FDA-approved TAMIFLU for Oral Suspension is commercially available.**

First, calculate the Total Volume of an oral suspension needed to be compounded and dispensed for each patient. The Total Volume required is determined by the weight of each patient. Refer to **Table 7**.

**Table 7 Volume of an Oral Suspension (15 mg/mL) Needed to be Compounded Based Upon the Patient's Weight**

Body Weight (kg)	Body Weight (lbs)	Total Volume to Compound per patient (mL)
≤15 kg	≤33 lbs	30 mL
16 to 23 kg	34 to 51 lbs	40 mL
24 to 40 kg	52 to 88 lbs	50 mL
≥41 kg	≥89 lbs	60 mL

Second, determine the number of capsules and the amount of vehicle (Cherry Syrup or Ora-Sweet SF) that are needed to prepare the Total Volume (calculated from Table 7: 30 mL, 40 mL, 50 mL, or 60 mL) of compounded oral suspension (15 mg/mL). Refer to **Table 8**.

**Table 8 Number of TAMIFLU 75 mg Capsules and Amount of Vehicle (Cherry Syrup OR Ora-Sweet SF) Needed to Prepare the Total Volume of a Compounded Oral Suspension (15 mg/mL)**

Total Volume of Compounded Oral Suspension needed to be Prepared	30 mL	40 mL	50 mL	60 mL
Required number of TAMIFLU 75 mg Capsules	6 capsules (450 mg oseltamivir)	8 capsules (600 mg oseltamivir)	10 capsules (750 mg oseltamivir)	12 capsules (900 mg oseltamivir)
Required volume of vehicle Cherry Syrup (Humco) OR Ora-Sweet SF (Paddock Laboratories)	29 mL	38.5 mL	48 mL	57 mL

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

1. Carefully separate the capsule body and cap and transfer the contents of the required number of TAMIFLU 75 mg Capsules into a clean mortar.
2. Triturate the granules to a fine powder.
3. Add one-third (1/3) of the specified amount of vehicle and triturate the powder until a uniform suspension is achieved.
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Add another one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar by a triturating motion and transfer the vehicle into the bottle.
6. Repeat the rinsing (Step 5) with the remainder of the vehicle.
7. Close the bottle using a child-resistant cap.
8. Shake well to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension. (Note: The active drug, oseltamivir phosphate, readily dissolves in the specified vehicles. The suspension is caused by some of the inert ingredients of TAMIFLU Capsules which are insoluble in these vehicles.)
9. Put an ancillary label on the bottle indicating "Shake Gently Before Use". [This compounded suspension should be gently shaken prior to administration to minimize the tendency for air entrapment, particularly with the Ora-Sweet SF preparation.]
10. Instruct the parent or guardian that any remaining material following completion of therapy must be discarded by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
11. Place an appropriate expiration date label according to storage condition (see below).

#### STORAGE OF THE PHARMACY-COMPOUNDED SUSPENSION:

**Refrigeration:** Stable for 5 weeks (35 days) when stored in a refrigerator at 2° to 8°C (36° to 46°F).

**Room Temperature:** Stable for five days (5 days) when stored at room temperature, 25°C (77°F).

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

Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, and drug name and any other required information to be in compliance with all State and Federal Pharmacy Regulations. **Refer to Table 9 for the proper dosing instructions.**

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

**Table 9                      Dosing Chart for Pharmacy-Compounded Suspension from TAMIFLU Capsules 75 mg**

Body Weight	Body Weight	Dose	Volume per Dose	Treatment Dose (for 5	Prophylaxis Dose (for
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(kg)	(lbs)	(mg)	15 mg/mL	days)	10 days)
≤15 kg	≤33 lbs	30 mg	2 mL	2 mL two times a day	2 mL once daily
16 to 23 kg	34 to 51 lbs	45 mg	3 mL	3 mL two times a day	3 mL once daily
24 to 40 kg	52 to 88 lbs	60 mg	4 mL	4 mL two times a day	4 mL once daily
≥41 kg	≥89 lbs	75 mg	5 mL	5 mL two times a day	5 mL once daily

*Note: 1 teaspoon = 5 mL*

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

#### HOW SUPPLIED

##### **TAMIFLU Capsules**

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

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

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

#### Storage

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

##### **TAMIFLU for Oral Suspension**

Supplied as a white powder blend for constitution to a white tutti-frutti-flavored suspension. Available in glass bottles containing approximately 33 mL of suspension after constitution. Each bottle delivers 25 mL of suspension equivalent to 300 mg oseltamivir base. Each bottle is supplied with a bottle adapter and 1 oral dispenser (NDC 0004-0810-95).

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### Storage

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

Store constituted suspension under refrigeration at 2° to 8°C (36° to 46°F). Do not freeze.

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## Patient Information

### TAMIFLU®

#### (oseltamivir phosphate)

#### R<sub>X</sub> ONLY

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

#### ***What is TAMIFLU?***

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

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

#### ***What is “Flu”?***

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

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

#### ***Should I get a flu shot?***

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

#### ***Who should not take TAMIFLU?***

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

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

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

### ***How should I take TAMIFLU?***

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

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

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

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 for Oral Suspension, your pharmacist will give you a dosing dispenser marked with three possible doses. Follow your healthcare 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 healthcare professional or pharmacist for advice on the proper dose.

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

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

### ***What are the possible side effects of TAMIFLU?***

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

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

People with the flu, particularly children, may be at an increased risk of self-injury and confusion shortly after taking TAMIFLU and should be closely monitored for signs of unusual behavior. A healthcare professional should be contacted immediately if the patient taking TAMIFLU shows any signs of unusual behavior.

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

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

### ***How and where should I store TAMIFLU?***

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

TAMIFLU for Oral Suspension should be stored under refrigeration at 36° to 46°F (2° to 8°C). 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 healthcare professional. You can ask your pharmacist or healthcare professional for information about TAMIFLU that is written for health professionals.

### DOSING INSTRUCTIONS FOR PATIENTS:

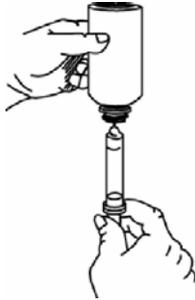
#### **How Do I Prepare TAMIFLU for Oral Suspension?**

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



- Shake closed bottle well for about 5 seconds before each use.
- Remove child-resistant cap.

- Before inserting the tip of the oral dispenser into bottle adapter, push the plunger completely down toward the tip of the oral dispenser. Insert tip firmly into opening of the bottle adapter.
- Turn the entire unit (bottle and oral dispenser) upside down.
- Pull the plunger out slowly until the desired amount of medication is withdrawn into the oral dispenser (see figure). The 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.

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

**Please follow instructions carefully to ensure proper dosing.**

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

NDA 21-087/S-040

NDA 21-246/S-027

Page 28

Distributed by:



**Pharmaceuticals**

Roche Laboratories Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

Licensors:

Gilead Sciences, Inc.

Foster City, California 94404

Revised: Month Year

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10 mil [REDACTED]

**Tamiflu**<sup>®</sup> (oseltamivir phosphate)  
Capsules 30 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT: [REDACTED] EXP: [REDACTED]  
N (01) 1.03.0004-0802-85.3

**Tamiflu**<sup>®</sup> (oseltamivir phosphate)  
Capsules 30 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT: [REDACTED] EXP: [REDACTED]  
N (01) 1.03.0004-0802-85.3

**Tamiflu**<sup>®</sup> (oseltamivir phosphate)  
Capsules 30 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT: [REDACTED] EXP: [REDACTED]  
N (01) 1.03.0004-0802-85.3

**Tamiflu**<sup>®</sup> (oseltamivir phosphate)  
Capsules 30 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT: [REDACTED] EXP: [REDACTED]  
N (01) 1.03.0004-0802-85.3

**Tamiflu**<sup>®</sup> (oseltamivir phosphate)  
Capsules 30 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT: [REDACTED] EXP: [REDACTED]  
N (01) 1.03.0004-0802-85.3

**Tamiflu**<sup>®</sup> (oseltamivir phosphate)  
Capsules 30 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT: [REDACTED] EXP: [REDACTED]  
N (01) 1.03.0004-0802-85.3

**Tamiflu**<sup>®</sup> (oseltamivir phosphate)  
Capsules 30 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT: [REDACTED] EXP: [REDACTED]  
N (01) 1.03.0004-0802-85.3

**Tamiflu**<sup>®</sup> (oseltamivir phosphate)  
Capsules 30 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT: [REDACTED] EXP: [REDACTED]  
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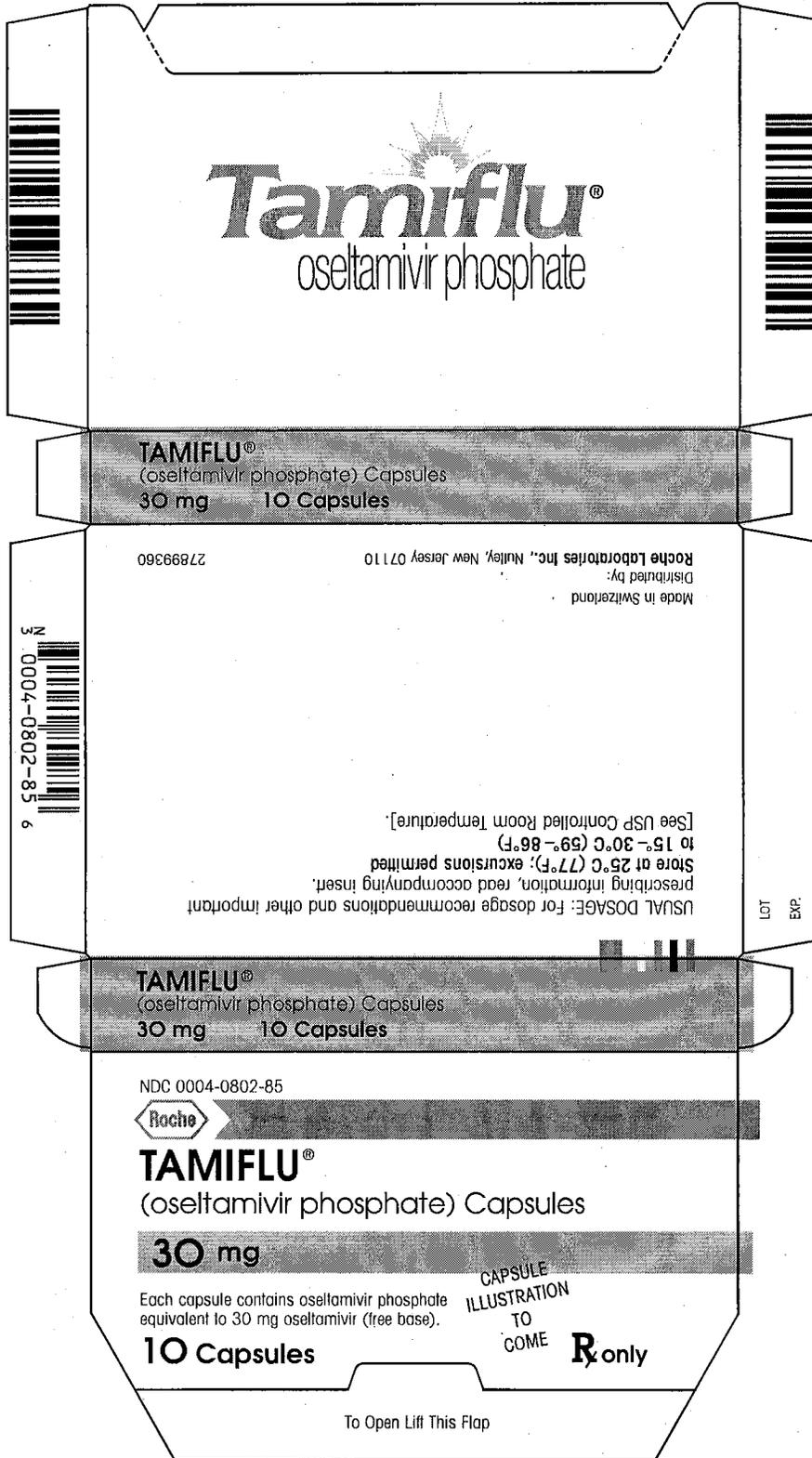
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Capsules 30 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT: [REDACTED] EXP: [REDACTED]  
N (01) 1.03.0004-0802-85.3

**Tamiflu**<sup>®</sup> (oseltamivir phosphate)  
Capsules 30 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT: [REDACTED] EXP: [REDACTED]  
N (01) 1.03.0004-0802-85.3

ACTUAL SIZE



[REDACTED]  
(01) 103 0004 0802 85 3



10 mil [REDACTED]

Tamiflu® (oseltamivir phosphate)  
Capsules 45 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT  
EXP  
N (01), 1.03.0004-0801-85.6

Tamiflu® (oseltamivir phosphate)  
Capsules 45 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT  
EXP  
N (01), 1.03.0004-0801-85.6

Tamiflu® (oseltamivir phosphate)  
Capsules 45 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT  
EXP  
N (01), 1.03.0004-0801-85.6

Tamiflu® (oseltamivir phosphate)  
Capsules 45 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT  
EXP  
N (01), 1.03.0004-0801-85.6

Tamiflu® (oseltamivir phosphate)  
Capsules 45 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT  
EXP  
N (01), 1.03.0004-0801-85.6

Tamiflu® (oseltamivir phosphate)  
Capsules 45 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT  
EXP  
N (01), 1.03.0004-0801-85.6

Tamiflu® (oseltamivir phosphate)  
Capsules 45 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT  
EXP  
N (01), 1.03.0004-0801-85.6

Tamiflu® (oseltamivir phosphate)  
Capsules 45 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT  
EXP  
N (01), 1.03.0004-0801-85.6

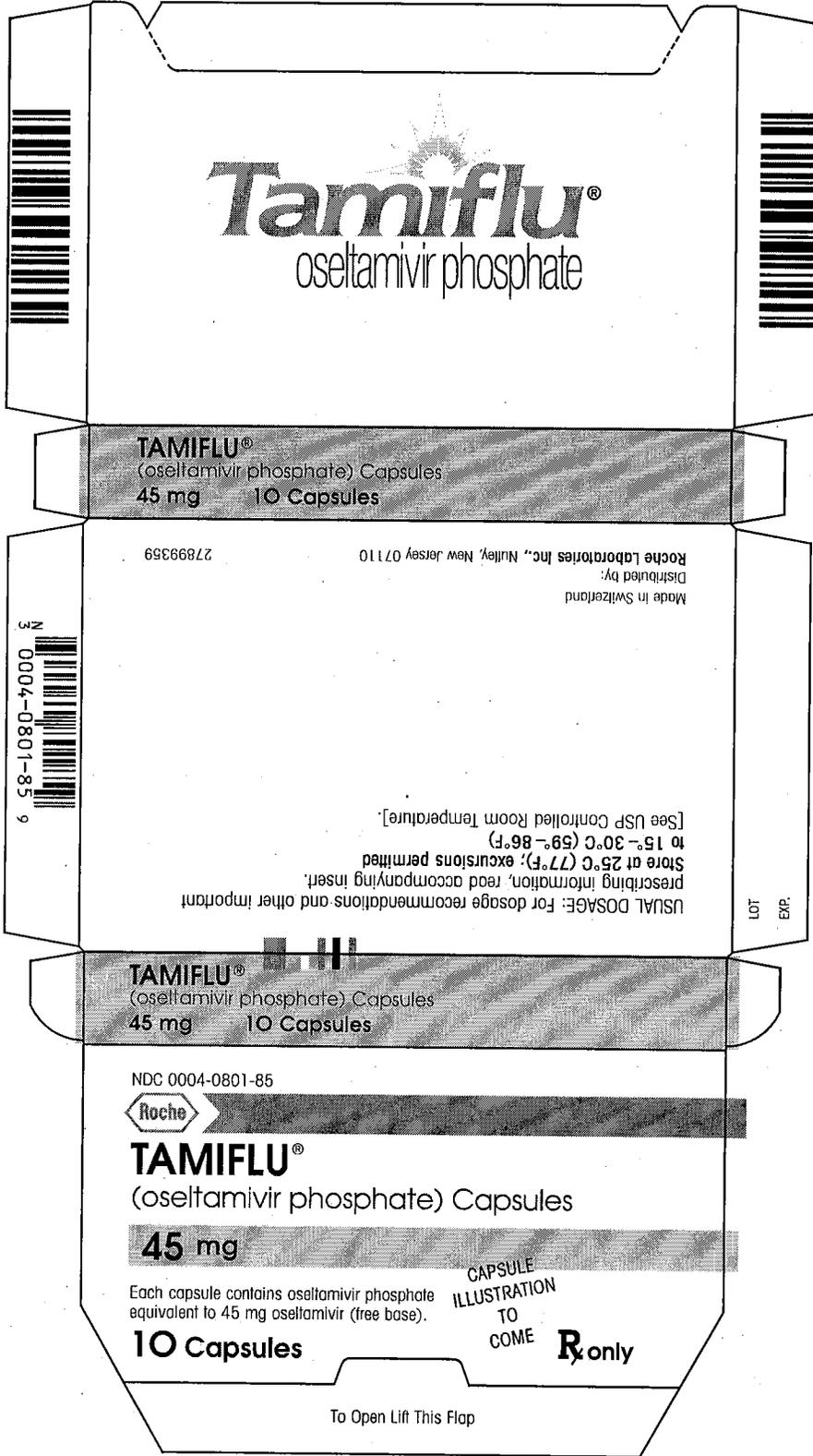
Tamiflu® (oseltamivir phosphate)  
Capsules 45 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT  
EXP  
N (01), 1.03.0004-0801-85.6

Tamiflu® (oseltamivir phosphate)  
Capsules 45 mg  
Distr. by: ROCHE LABORATORIES INC.  
NUTLEY, NJ 07110  
LOT  
EXP  
N (01), 1.03.0004-0801-85.6

ACTUAL SIZE



(01) 103 0004 0801 85 6



27899363-L (D) 06June07:27899363-L (D) 06June07 6/6/07 2:32 PM

NDC 0004-0803-07

**TAMIFLU® 30 mg**  
(oseltamivir phosphate)  
Capsules

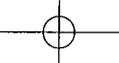
Each capsule contains  
oseltamivir phosphate  
equivalent to 30 mg oseltamivir.

**Rx only**

10 Capsules

USUAL DOSAGE: 1 Capsule  
twice per day for 5 days.

LOT  
EXP.

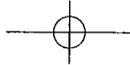


TAMIFLU®  
30 mg  
10 Capsules

TAMIFLU®  
30 mg  
10 Capsules

Made in Switzerland  
Distributed by:  
Roche Laboratories Inc., Nutley, NJ 07110

**WARNING: KEEP OUT OF CHILDREN'S REACH**  
Store at 25°C (77°F); excursions  
permitted to 15°-30°C (59°-86°F)  
[see USP Controlled Room Temperature].  
**FOR DEPT. OF DEFENSE STOCKPILE USE ONLY**  
27899363



27899361-L (D) 06June07:27899361-L (D) 06June07 6/6/07 2:30 PM

NDC 0004-0802-06

LOT  
EXP.

**TAMIFLU® 30 mg**  
(oseltamivir phosphate)

Capsules

Each capsule contains  
oseltamivir phosphate  
equivalent to 30 mg oseltamivir.

**Rx only**

**10 Capsules**

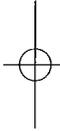
USUAL DOSAGE: 1 Capsule  
twice per day for 5 days.

Made in Switzerland  
Distributed by:  
Roche Laboratories Inc., Nutley, NJ 07110

**WARNING: KEEP OUT OF CHILDREN'S REACH**

Store at 25°C (77°F); excursions  
permitted to 15°-30°C (59°-86°F)  
[see USP Controlled Room Temperature].

27899361



27899362-L (D) 05June07:27899362-L (D) 28Feb07 6/6/07 2:31 PM E

NDC 0004-0802-08

**TAMIFLU® 30 mg**  
(oseltamivir phosphate)  
Capsules

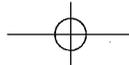
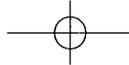
Each capsule contains  
oseltamivir phosphate  
equivalent to 30 mg oseltamivir.

**10 Capsules**

**USUAL DOSAGE:** 1 Capsule  
twice per day for 5 days.

LOT  
EXP

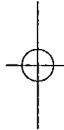
27899362



TAMIFLU®  
30 mg  
10 Capsules

TAMIFLU®  
30 mg  
10 Capsules

Made in Switzerland  
Distributed by  
Roche Laboratories Inc., Nutley, NJ 07110



**WARNING: KEEP OUT OF CHILDREN'S REACH**  
Store at 25°C (77°F); excursions  
permitted to 15°-30°C (59°-86°F)  
[See USP Controlled Room Temperature].  
FOR STRATEGIC NATIONAL STOCKPILE USE ONLY

27899366-L (D) 05June07 : 27899366-L (D) 05June07 6/6/07 2:34 PM

NDC 0004-0801-07

**TAMIFLU® 45 mg**  
(oseltamivir phosphate)  
Capsules

Each capsule contains  
oseltamivir phosphate  
equivalent to 45 mg oseltamivir.

**10 Capsules**

**USUAL DOSAGE:** 1 Capsule  
twice per day for 5 days.

LOT  
EXP.

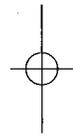
Made in Switzerland  
Roche Pharmaceuticals Inc., Nutley, NJ 07110



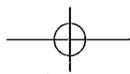
TAMIFLU®  
45 mg  
10 Capsules

TAMIFLU®  
45 mg  
10 Capsules

Made in Switzerland  
Roche Pharmaceuticals Inc., Nutley, NJ 07110



**WARNING: KEEP OUT OF CHILDREN'S REACH**  
Store at 25°C (77°F); excursions  
permitted to 15°-30°C (59°-86°F)  
(see USP Controlled Room Temperature).  
**FOR DEPT. OF DEFENSE STOCKPILE USE ONLY**  
27899366



27899364-L (D) 05June07:27899364-L (D) 05June07 6/6/07 2:33 PM

NDC 0004-0801-06

LOT  
EXP

**TAMIFLU® 45 mg**  
(oseltamivir phosphate)  
Capsules

Each capsule contains  
oseltamivir phosphate  
equivalent to 45 mg oseltamivir.

**R only**

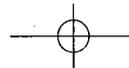
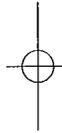
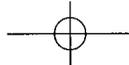
10 Capsules

USUAL DOSAGE: 1 Capsule  
twice per day for 5 days.

Made in Switzerland  
Distributed by  
Roche Laboratories Inc., Nutley, NJ 07110

**WARNING: KEEP OUT OF CHILDREN'S REACH**  
Store at 25°C (77°F); excursions  
permitted to 15°–30°C (59°–86°F)  
(see USP Controlled Room Temperature).

27899364





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this page is the manifestation of the electronic signature.**  
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/s/

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Debra Birnkrant  
7/2/2007 03:58:54 PM  
NDA 21-246, 21-087,

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021087/S-040**

**MEDICAL REVIEW(S)**

**Medical Officer Review**  
**NDA 21-087, SCF 040 (Chemistry Supplement with labeling)**  
**NDA 21-246, SCF 027 (Chemistry Supplement with labeling)**

Date Submitted: March 8, 2007

Date Received: March 9, 2007

Date Reviewed: June 11, 2007

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

Product: Tamiflu® (oseltamivir phosphate) 30 and 45 mg capsules

(b) (4)

## **I. Materials Submitted and Reviewed:**

This submission contains one volume of CMC data and labeling proposals for 2 new sizes of Tamiflu capsules, 30 and 45 mg. According to the applicant, these new capsules are (b) (4) in their active and inactive ingredients to the currently marketed 75 mg capsule and are intended for use in the pediatric population. They might also be used in patients with renal impairment who require dose adjustment. The capsule shells for the new sizes are smaller than that for the 75 mg capsule (b) (4). The capsules use an identical manufacturing process as the currently available 75 mg capsules with smaller fill volumes in the smaller capsules. In addition, the new capsules use variations of the same color scheme (all gray or all yellow shells) as the commercially available capsules (gray/yellow shells). The 30 mg and 45 mg capsules will be packaged for commercial use using the same blister packs as the 75 mg capsules. For potential stockpile use, the new strengths will be packaged in the same HDPE bottles holding 10 capsules as for the 75 mg capsules. Three-month stability data for the new formulations was submitted during the review cycle. For a complete review of the CMC data, please refer to the Chemistry Review conducted by Dr. Joel (Steve) Hathaway. This Medical Officer reviewed the clinical rationale for the smaller size capsules and the proposed labeling.

## **II. Clinical Rationale:**

Tamiflu, manufactured and distributed by Hoffman-La Roche Inc., is an influenza neuraminidase inhibitor. It has been shown in clinical trials to be safe and effective in the treatment of uncomplicated influenza in patients > 1 year of age. In otherwise healthy patients with seasonal influenza, treatment with Tamiflu shortened the duration of symptoms by about 1.5 days and decreased the self-reported severity of those symptoms. Tamiflu has also been shown to be effective as post-exposure prophylaxis in the

household setting or as pre-exposure prophylaxis in the community/institutional outbreak setting. The safety profile of Tamiflu is generally acceptable, although recent spontaneous Adverse Event reports of abnormal and self-injurious behavior in pediatric patients (primarily in Japan) continue to be evaluated.

The pediatric clinical trials were conducted using a Tamiflu dose of 2 mg/kg twice daily for 5 days. Current dosing recommendations for Tamiflu in pediatric patients  $\leq$  40 kg are based on weight but were collapsed into weight strata. Dosing is divided into 4 weight strata:  $\leq$  15 kg (30 mg), > 15 kg to 23 kg (45 mg), > 23 kg to 40 kg (60 mg), and > 40 kg (75 mg, adult dose) given either twice daily for 5 days (treatment regimen) or once daily for 10 days (post-exposure prophylaxis). The commercially available Tamiflu for Oral Suspension contains 12 mg/mL and is packaged with a dosing device marked at 30 mg and 45 mg. The dosing device is not calibrated in mL.

Over the last 3 years, HHS and other branches of the US government have become concerned that there is increasing likelihood of an influenza pandemic emerging. Most notable are the > 300 human cases reported worldwide of avian influenza due to influenza A/H5N1. To date, there has been little to no evidence of human-to-human spread of this strain but sporadic cases have been identified in many countries in Southeast Asia and Africa. Tamiflu has been shown to have activity *in vitro* and in animal models against strains of influenza A/H5N1 and has been used in the clinical setting in some of these sporadic cases. However, no clinical trials providing evidence of effectiveness of Tamiflu in this setting have been done and none are likely to be available in the near future.

In preparation for a possible influenza pandemic, the US government has developed a plan to provide Tamiflu to up to 25% of the US population. Much of this stockpile is maintained at the Strategic National Stockpile (SNS), administered by the CDC. Because of the difficulty of storage and the shorter shelf-life of Tamiflu for Oral Suspension, the SNS has acquired relatively little Tamiflu in a formulation that will be suitable for dispensing to pediatric patients < 40 kg. A solid oral formulation could be more easily maintained in storage and more easily distributed in the event of a public health emergency. As part of pandemic influenza preparedness planning, the FDA and HHS requested that Roche consider the feasibility of producing smaller size capsules that could be administered to pediatric patients. This submission is the end result of this effort by the applicant to provide appropriate dosing for all age groups in the event of an influenza pandemic. It also provides an alternate formulation for pediatric patients with seasonal influenza who are able to swallow capsules and for patients with reduced creatinine clearance who may need dose adjustment.

### **III. Labeling Review:**

The following section provides a listing of the significant revisions to the Tamiflu label resulting from this supplement along with comments forwarded to the applicant.

1. [REDACTED] (b) (4)

2. The technical description of the 30 mg and 45 mg capsules has been incorporated into the DESCRIPTION section of the label.

3. The recommended dose of Tamiflu for treatment or prophylaxis of influenza in pediatric patients is contained in Tables 5 and 6, respectively. The recommended dosing using the capsule formulations are incorporated into the tables as an additional column "Number of Tamiflu Capsules Needed to Obtain the Recommended Doses..." Table 5, reproduced below, displays the recommended 5-day BID treatment regimen for either suspension or capsules. Table 6 contains similar recommendations for the 10-day, once daily prophylaxis regimen.

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

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

4. The recommended dose of Tamiflu for prophylaxis in patients with creatinine clearance between 10 and 30 mL/minute has been modified allowing use of any formulation that will supply 30 mg daily (previously the Oral Suspension was specified).

5. The new size capsules have been added to the HOW SUPPLIED section of the label. [REDACTED] (b) (4)

(b) (4)

#### **IV. Medical Officer's Recommendations:**

From a clinical perspective, the approval of the Tamiflu 30 mg and 45 mg capsules will provide additional dosing options for pediatric patients < 40 kg and for some patients with impaired renal function. Availability of these new formulations will enhance dosing for both seasonal influenza and could potentially improve storage and distribution in the event of a public health emergency. This supplement should be approved with the minor labeling revisions noted above. The applicant has been asked to provide materials educating health care providers on the availability and proper usage of the new formulations.

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

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/s/

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Linda Lewis  
6/18/2007 05:12:47 PM  
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021087/S-040**

**CHEMISTRY REVIEW(S)**

**OFFICE ON NEW DRUG QUALITY ASSESSMENT  
DIVISION OF POST-MARKETING EVALUATION, BRANCH VIII**

Review of Chemistry, Manufacturing, and Controls  
for the Division of Antiviral Drug Products, HFD-530

**NDA #:** 21-087, 21-246      **CHEM.REVIEW #:** 1      **REVIEW DATE:** 02-JUL-2007

<b><u>SUBMISSION/TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
NDA 21-087/SCF-040	08-MAR-2007	09-MAR-2007	23-MAR-2007
NDA 21-087/SCF-040(BL)	08-MAR-2007	09-MAR-2007	23-MAR-2007
NDA 21-087/SCF-040(BC)	04-JUN-2007	04-JUN-2007	04-JUN-2007
NDA 21-087/SCF-040(BL)	21-JUN-2007	21-JUN-2007	21-JUN-2007
NDA 21-246/SCF-027	08-MAR-2007	09-MAR-2007	23-MAR-2007
NDA 21-246/SCF-027(BL)	08-MAR-2007	09-MAR-2007	23-MAR-2007
NDA 21-246/SCF-027(BC)	04-JUN-2007	04-JUN-2007	04-JUN-2007
NDA 21-246/SCF-027(BL)	21-JUN-2007	21-JUN-2007	21-JUN-2007

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

Arun Chalgeri, Ph.D.  
Program Manager, Drug Regulatory Affairs  
(973) 562-5550 fax (973) 562-3700

**DRUG PRODUCT NAME**

Proprietary:

Nonproprietary/USAN:

Code Names/#'s:

Chemical Type/

Therapeutic Class:

TAMIFLU® Capsules

oseltamivir phosphate

Ethyl ester prodrug

Antiviral; influenza virus neuraminidase inhibitor

**ANDA Suitability Petition/DESI/Patent Status:**

N/A

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

**DOSAGE FORM:**

Capsules

**STRENGTHS:**

75mg (as free base)

**ROUTE OF ADMINISTRATION:**

Oral

**DISPENSED:**

X  Rx      OTC

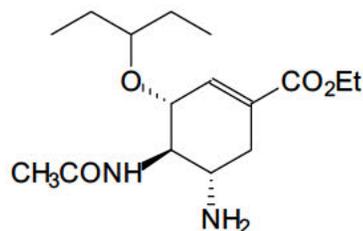
**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,**

**MOL.WT:**

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

Molecular Formula:      C<sub>16</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>·PO<sub>4</sub>

Molecular Weight: 410.4 (312.4 free base)



**SUPPORTING DOCUMENTS:**

Medical Officer's review of proposed labeling, dated 11-JUN-2007.

[Redacted] (b) (4)

**REMARKS/COMMENTS:**

This "Supplement - Prior Approval" submission provides for two new drug product strengths, 30mg and 45mg, for TAMIFLU® Capsules. These strengths are intended to permit dosing in amounts appropriate to pediatric patients when Tamiflu® for Oral Suspension is unavailable. This supplement and NDA 21-246 / SCF-027 are bundled because Tamiflu® for Oral Suspension shares labeling with the capsule dosage form, and the package insert has been revised to include the new dosing regimens and forms. These supplements were also assigned for review to clinical pharmacology, which reviewed and granted a waiver for *in vivo* bioequivalence data for the Tamiflu® 30mg and 45mg capsules, in a letter to the sponsor dated 22-DEC-2006.

The supplement contains a summary, pharmaceutical development report, and detailed descriptions of the components and composition, manufacturing, packaging, container-closure system, specification and analytical methods, methods validation, batch analysis results, stability data, and claim of categorical exclusion from the environmental assessment. Stability data for the exhibit batches for one month of storage were provided in the initial submission, with an update to six months of data submitted 06-JUN-2007.

Draft labeling was provided in the amendment. Multiple changes to the draft labeling were recommended to the applicant; [Redacted] (b) (4), [Redacted] (b) (4), Lists of ingredients for the 30mg and 45mg capsules were added to the Description section; [Redacted] (b) (4). The new strengths were also added to the How Supplied section, along with new NDC numbers.

This supplement was assigned Review Path 4 - High Risk, Single Reviewer by the PAL.

**NDA 21-087 / SCF-040**  
**NDA 21-246 / SCF-027**  
**TAMIFLU® (oseltamivir phosphate capsules) Capsules**  
**Hoffmann-La Roche Inc.**

**Page 3 of 11**

**CONCLUSIONS & RECOMMENDATIONS:**

**APPROVAL**

Approval is recommended for this supplement.

*(see attached electronic signature page)*

---

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

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

**filename:** C:\Documents and Settings\hathaways\My Documents\MSWordDocs\NDA  
Reviews\SuppNDAs\21087\N21087r.scm.040.doc

**Approval**

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/s/

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Steve Hathaway  
7/2/2007 10:05:28 AM  
CHEMIST  
New dosing strengths - AP recommended  
For your concurrence

Hasmukh Patel  
7/2/2007 10:16:37 AM  
CHEMIST

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 021087/S-040**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



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

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FACSIMILE TRANSMITTAL SHEET

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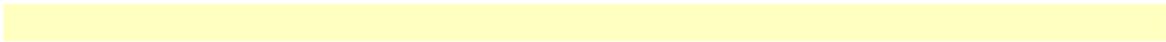
DATE: June 25, 2007

To: Ellen Carey, PharmD, Sr. Program Director, 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: 301-796-9883
Phone number: 973-562-3757	Phone number: 301-796-0777

Subject: Labeling comments for NDA 21-087/S-040 & NDA 21-246/S-027.

Total no. of pages including cover: 2

Comments:



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Document to be mailed:  YES  NO

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** June 25, 2007

**To:** Ellen Carey, PharmD, Senior Program Director, Drug Regulatory Affairs

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

**NDA:** 21-087/S-040  
21-246/S-027

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

**From:** Linda Lewis, MD, Acting Medical Officer Team Leader, DAVP

**Subject:** Labeling comments for your supplements 21-087/S-040 & 21-246/S-027 for 30 mg and 45 mg Tamiflu® capsules.

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In our most recent review of the proposed labeling for Tamiflu 30 mg and 45 mg capsules we noted that there are no instructions on how to administer the capsules to pediatric patients who can not swallow capsules. We propose including labeling for this in the Dosage and Administration section. An example of possible language might be:

For pediatric patients who can not swallow capsules, Tamiflu for Oral Suspension is the preferred formulation. If the for Oral Suspension product is not available, capsules may be opened and mixed with (b) (4)

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/s/

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Jeff O'Neill  
6/25/2007 04:36:12 PM  
CSO

Labeling comments 21-087/S-040 & 21-246/S-027

Linda Lewis  
6/25/2007 05:18:32 PM  
MEDICAL OFFICER



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

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FACSIMILE TRANSMITTAL SHEET

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DATE: June 15, 2007

To: Ellen Carey, PharmD, Sr. Program Director, 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: 301-796-9883
Phone number: 973-562-3757	Phone number: 301-796-0777

Subject: Labeling comments for NDA 21-087/S-040 & NDA 21-246/S-027.

Total no. of pages including cover: 2

Comments:



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Document to be mailed:  YES  NO

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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** June 15, 2007

**To:** Ellen Carey, PharmD, Senior Program Director, Drug Regulatory Affairs

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

**NDA:** 21-087/S-040  
21-246/S-027

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

**From:** Linda Lewis, MD, Acting Medical Officer Team Leader, DAVP  
Steve Hathaway, PhD, Chemistry Reviewer, ONDQA, DPME

**Subject:** Labeling comments for your supplements 21-087/S-040 & 21-246/S-027 for 30 mg and 45 mg Tamiflu® capsules.

- The new size capsules have been added to the **HOW SUPPLIED** section of the label. (b) (4)  

- The statement above Table 6, **Oral Dose of TAMIFLU for Prophylaxis of Influenza in Pediatric Patients by Weight**, should contain the same language as the statement above Table 5. Please add back the sentence "TAMIFLU for Oral Suspension may also be used by patients who cannot swallow a capsule" for consistency.

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/

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Jeff O'Neill  
6/15/2007 01:45:04 PM  
CSO

Labeling comments for S-040 & S-027. Hard copy sign-off  
6/15/07

Linda Lewis  
6/15/2007 01:54:42 PM  
MEDICAL OFFICER



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE: June 1, 2007**

<b>To: Ellen Carey, PharmD, Sr. Program Director, Drug Regulatory Affairs</b>	<b>From: Jeff D. O'Neill, ACRN Regulatory Health Project Manager</b>
<b>Company: Hoffmann - La Roche, Inc.</b>	<b>Division of Antiviral Drug Products</b>
<b>Fax number: 973-562-3700</b>	<b>Fax number: 301-796-9883</b>
<b>Phone number: 973-562-3757</b>	<b>Phone number: 301-796-0777</b>

**Subject:**

**Total no. of pages including cover: 2**

**Comments:**



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**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**Date:** June 1, 2007

**To:** Ellen Carey, PharmD, Senior Program Director, Drug Regulatory Affairs

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

**NDA:** 21-087/S-040  
21-246/S-027

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

**From:** Linda Lewis, MD, Acting Medical Officer Team Leader, DAVP

**Subject:** Request for information regarding your supplement for the 30 mg and 45 mg Tamiflu capsules.

- 
- Please submit 3-month stability data for capsules packaged in blisters.
  - Please submit revised draft PI, carton, [REDACTED] (b) (4)  
[REDACTED] The CDER Data Standards Manual does not include pediatric as an acceptable dosage form. The acceptable dosage form for this drug product is "Capsules".
  - Please advise us of your plans regarding notification to providers for the new 30 mg and 45 mg capsules.

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/s/

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Jeff ONeill  
6/1/2007 02:14:19 PM  
CSO

Linda Lewis  
6/1/2007 02:40:19 PM  
MEDICAL OFFICER



NDA 21-087/S-040  
NDA 21-246/S-027

**PRIOR APPROVAL SUPPLEMENT**

Hoffmann-La Roche, Inc.  
Attention: Arun Chalgeri, Ph.D.  
Program Manager  
340 Kingsland Street  
Nutley, NJ 07110

Dear Dr. Chalgeri:

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

Application	Product	Supplement
NDA 21-087	Tamiflu® (oseltamivir phosphate) Capsules	S-040
NDA 21-246	Tamiflu® (oseltamivir phosphate) for Oral Suspension	S-027

Date of supplement: March 8, 2007

Date of receipt: March 9, 2007

This supplemental application provides for two new capsule strengths, 30 mg and 45 mg, which are intended for pediatric use.

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 May 8, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 9, 2007.

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

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

NDA 21-087/S-040  
NDA 21-246/S-027  
Page 2

If you have any questions, call me at (301) 796-1345.

Sincerely,

*{See appended electronic signature page}*

Valerie Jimenez, MS  
Senior Regulatory Project Manager  
Branch 8, Division of Post-Marketing Evaluation  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Valerie Jimenez  
4/2/2007 02:35:06 PM



NDA 21-087/S-040  
NDA 21-246/S-027

**PRIOR APPROVAL SUPPLEMENT**

Hoffmann-La Roche, Inc.  
Attention: Arun Chalgeri, Ph.D.  
Program Manager  
340 Kingsland Street  
Nutley, NJ 07110

Dear Dr. Chalgeri:

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

Application	Product	Supplement
NDA 21-087	Tamiflu® (oseltamivir phosphate) Capsules	S-040
NDA 21-246	Tamiflu® (oseltamivir phosphate) for Oral Suspension	S-027

Date of supplement: March 8, 2007

Date of receipt: March 9, 2007

This supplemental application provides for 1 month stability data for capsules packaged in blisters at accelerated and long-term storage conditions.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 8, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 9, 2007.

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

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

NDA 21-087/S-040  
NDA 21-246/S-027  
Page 2

If you have any questions, call me at (301) 796-1345.

Sincerely,

*{See appended electronic signature page}*

Valerie Jimenez, MS  
Senior Regulatory Project Manager  
Branch 8, Division of Post-Marketing Evaluation  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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Valerie Jimenez  
3/27/2007 01:07:53 PM