TAMIFLU®

(oseltamivir phosphate)

CAPSULES

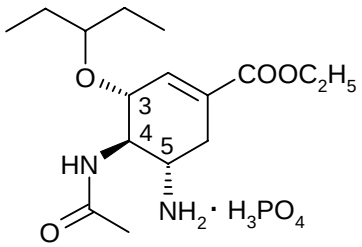
AND FOR ORAL SUSPENSION

R_X only

DESCRIPTION

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

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



MICROBIOLOGY

Mechanism of Action

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

Antiviral Activity In Vitro

The antiviral activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of oseltamivir carboxylate required for inhibition of influenza virus were highly variable depending on the assay method used and the virus tested. The 50% and 90% inhibitory concentrations (IC_{50} and IC_{90}) were in the range of 0.0008 μM to >35 μM and 0.004 μM to >100 μM, respectively (1 μM=0.284 μg/mL). The relationship between the in vitro antiviral activity in cell culture and the inhibition of influenza virus replication in humans has not been established.

Resistance

Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have been recovered in vitro by passage of virus in the presence of increasing concentrations of oseltamivir carboxylate. Genetic analysis of these isolates showed that reduced susceptibility to oseltamivir carboxylate is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both. Resistance mutations selected in vitro in neuraminidase are I222T and H274Y in influenza A N1 and I222T and R292K in influenza A N2. Mutations E119V, R292K and R305Q have been selected in avian influenza A neuraminidase N9. Mutations A28T and R124M have been selected in the hemagglutinin of influenza A H3N2 and mutation H154Q in the hemagglutinin of a reassortant human/avian virus H1N9.

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

In clinical studies of postexposure and seasonal prophylaxis, determination of resistance was limited by the low overall incidence rate of influenza infection and prophylactic effect of TAMIFLU.

Cross-resistance

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

Immune Response

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

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption and Bioavailability

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure after oral dosing (see **Table 1**).

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

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

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

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

Distribution

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

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

Metabolism

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

Elimination

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

Special Populations

Renal Impairment

Administration of 100 mg of oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. Oseltamivir carboxylate exposures in patients with normal and abnormal renal function administered various dose regimens of oseltamivir are described in **Table 2**.

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

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

*Observed values. All other values are predicted.

AUC normalized to 48 hours.

Pediatric Patients

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

Geriatric Patients

Exposure to oseltamivir carboxylate at steady-state was 25% to 35% higher in geriatric patients (age range 65 to 78 years) compared to young adults given comparable doses of

oseltamivir. Half-lives observed in the geriatric patients were similar to those seen in young adults. Based on drug exposure and tolerability, dose adjustments are not required for geriatric patients for either treatment or prophylaxis (see **DOSAGE AND ADMINISTRATION: Special Dosage Instructions**).

INDICATIONS AND USAGE

Treatment of Influenza

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

Prophylaxis of Influenza

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

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

Description of Clinical Studies: Studies in Naturally Occurring Influenza

Treatment of Influenza

Adult Patients

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

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

TAMIFLU was started within 40 hours of onset of symptoms. Subjects participating in the trials were required to self-assess the influenza-associated symptoms as "none", "mild", "moderate" or "severe". Time to improvement was calculated from the time of treatment initiation to the time when all symptoms (nasal congestion, sore throat, cough, aches, fatigue, headaches, and chills/sweats) were assessed as "none" or "mild". In both studies, at the recommended dose of TAMIFLU 75 mg twice daily for 5 days, there was a 1.3 day reduction in the median time to improvement in influenza-infected subjects receiving TAMIFLU compared to subjects receiving placebo. Subgroup analyses of these studies by gender showed no differences in the treatment effect of TAMIFLU in men and women.

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

Geriatric Patients

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

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

Pediatric Patients

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

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

Prophylaxis of Influenza

Adult Patients

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

In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults (aged 13 to 65 years), TAMIFLU 75 mg once daily taken for 42 days during a community outbreak reduced the incidence of laboratory-confirmed clinical influenza from 4.8% (25/519) for the placebo group to 1.2% (6/520) for the TAMIFLU group.

In a seasonal prophylaxis study in elderly residents of skilled nursing homes, TAMIFLU 75 mg once daily taken for 42 days reduced the incidence of laboratory-confirmed clinical influenza from 4.4% (12/272) for the placebo group to 0.4% (1/276) for the TAMIFLU group. About 80% of this elderly population were vaccinated, 14% of subjects had chronic airway obstructive disorders, and 43% had cardiac disorders.

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

Pediatric Patients

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

CONTRAINDICATIONS

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

PRECAUTIONS

General

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

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

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

Efficacy of TAMIFLU in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population. No information is available regarding treatment of influenza in patients with any medical

condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalization.

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

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

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. TAMIFLU has not been shown to prevent such complications.

Hepatic Impairment

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

Renal Impairment

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

Serious Skin/Hypersensitivity Reactions

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

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 ($AUC_{0\text{-}24h}$) of oseltamivir carboxylate.

Pregnancy

Pregnancy Category C

There are insufficient human data upon which to base an evaluation of risk of TAMIFLU to the pregnant woman or developing fetus. Studies for effects on embryo-fetal development were conducted in rats (50, 250, and 1500 mg/kg/day) and rabbits (50, 150, and 500 mg/kg/day) by the oral route. Relative exposures at these doses were, respectively, 2, 13, and 100 times human exposure in the rat and 4, 8, and 50 times human exposure in the rabbit. Pharmacokinetic studies indicated that fetal exposure was seen in both species. In the rat study, minimal maternal toxicity was reported in the 1500 mg/kg/day group. In the rabbit study, slight and marked maternal toxicities were observed, respectively, in the 150 and 500 mg/kg/day groups. There was a dose-dependent increase in the incidence rates of a variety of minor skeletal abnormalities and variants in the exposed offspring in these studies. However, the individual incidence rate of each skeletal abnormality or variant remained within the background rates of occurrence in the species studied.

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

Nursing Mothers

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

Geriatric Use

The safety of TAMIFLU has been established in clinical studies which enrolled 741 subjects (374 received placebo and 362 received TAMIFLU). Some seasonal variability was noted in the clinical efficacy outcomes (see **INDICATIONS AND USAGE:**

Description of Clinical Studies: Studies in Naturally Occurring Influenza: Treatment of Influenza: Geriatric Patients).

Safety and efficacy have been demonstrated in elderly residents of nursing homes who took TAMIFLU for up to 42 days for the prevention of influenza. Many of these individuals had cardiac and/or respiratory disease, and most had received vaccine that season (see **INDICATIONS AND USAGE: Description of Clinical Studies: Studies in Naturally Occurring Influenza: Prophylaxis of Influenza: Adult Patients**).

Pediatric Use

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

ANIMAL TOXICOLOGY

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

ADVERSE REACTIONS

Treatment Studies in Adult Patients

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

Adverse events that occurred with an incidence of ≥1% in 1440 patients taking placebo or TAMIFLU 75 mg twice daily in adult phase III treatment studies are shown in **Table 3**. This summary includes 945 healthy young adults and 495 “at risk” patients (elderly patients and patients with chronic cardiac or respiratory disease). Those events reported

numerically more frequently in patients taking TAMIFLU compared with placebo were nausea, vomiting, bronchitis, insomnia, and vertigo.

Prophylaxis Studies in Adult Patients

A total of 4187 subjects (adolescents, healthy adults and elderly) participated in phase III prophylaxis studies, of whom 1790 received the recommended dose of 75 mg once daily for up to 6 weeks. Adverse events were qualitatively very similar to those seen in the treatment studies, despite a longer duration of dosing (see **Table 3**). Events reported more frequently in subjects receiving TAMIFLU compared to subjects receiving placebo in prophylaxis studies, and more commonly than in treatment studies, were aches and pains, rhinorrhea, dyspepsia and upper respiratory tract infections. However, the difference in incidence between TAMIFLU and placebo for these events was less than 1%. There were no clinically relevant differences in the safety profile of the 942 elderly subjects who received TAMIFLU or placebo, compared with the younger population.

Table 3 Most Frequent Adverse Events in Studies in Naturally Acquired Influenza in Patients 13 Years of Age and Older

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

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

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

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

Treatment Studies in Pediatric Patients

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

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

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

Prophylaxis in Pediatric Patients

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

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

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

Lymphadenopathy	8	(2%)	5	(1%)	-	-
Tympanic membrane disorder	6	(1%)	5	(1%)	-	-

[a] Pooled data from Phase III trials of TAMIFLU treatment of naturally acquired influenza.

[b] A randomized, open-label study of household transmission in which household contacts received either prophylaxis or no prophylaxis but treatment if they became ill. Only contacts who received prophylaxis or who remained on no prophylaxis are included in this table.

[c] Unit dose = age-based dosing

Age	Prophylaxis (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 ≥1% in the oseltamivir 75 mg bid group.

Observed During Clinical Practice

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

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

Dermatologic: Dermatitis, rash, eczema, urticaria, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis (see **PRECAUTIONS**)

Digestive: Hepatitis, liver function tests abnormal

Cardiac: Arrhythmia

Neurologic: Seizure, confusion

Metabolic: Aggravation of diabetes

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

Standard Dosage – Treatment of Influenza:

Adults and Adolescents

The recommended oral dose of TAMIFLU for treatment of influenza in adults and adolescents 13 years and older is 75 mg twice daily for 5 days. Treatment should begin within 2 days of onset of symptoms of influenza.

Pediatric Patients

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

The recommended oral dose of TAMIFLU Oral Suspension for pediatric patients 1 year and older or adult patients who cannot swallow a capsule is:

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

An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser provided is lost or damaged, another dosing syringe or other device may be used to deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for >15 to 23 kg, 5.0 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

Standard Dosage – Prophylaxis of Influenza:

Adults and Adolescents

The recommended oral dose of TAMIFLU for prophylaxis of influenza in adults and adolescents 13 years and older following close contact with an infected individual is 75 mg once daily for at least 10 days. Therapy should begin within 2 days of exposure. The recommended dose for prophylaxis during a community outbreak of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks. The duration of protection lasts for as long as dosing is continued.

Pediatric Patients

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

The recommended oral dose of TAMIFLU Oral Suspension for pediatric patients 1 year and older following close contact with an infected individual is:

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

An oral dosing dispenser with 30 mg, 45 mg, and 60 mg graduations is provided with the oral suspension; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser. In the event that the dispenser provided is lost or damaged, another dosing syringe or other device may be used to deliver the following volumes: 2.5 mL (1/2 tsp) for children ≤15 kg, 3.8 mL (3/4 tsp) for >15 to 23 kg, 5.0 mL (1 tsp) for >23 to 40 kg, and 6.2 mL (1 1/4 tsp) for >40 kg.

Prophylaxis in pediatric patients following close contact with an infected individual is recommended for 10 days. Prophylaxis in patients 1 to 12 years of age has not been evaluated for longer than 10 days duration. Therapy should begin within 2 days of exposure.

Special Dosage Instructions

Hepatic Impairment

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

Renal Impairment

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

Treatment of Influenza

Dose adjustment is recommended for patients with creatinine clearance between 10 and 30 mL/min receiving TAMIFLU for the treatment of influenza. In these patients it is recommended that the dose be reduced to 75 mg of TAMIFLU once daily for 5 days. No recommended dosing regimens are available for patients undergoing routine hemodialysis and continuous peritoneal dialysis treatment with end-stage renal disease.

Prophylaxis of Influenza

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

Geriatric Patients

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

Preparation of TAMIFLU Oral Suspension

It is recommended that TAMIFLU Oral Suspension be constituted by the pharmacist prior to dispensing to the patient:

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

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

The constituted TAMIFLU 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 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 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 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 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 5**.

Table 5 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 or less	33 lbs or less	30 mL
16 to 23 kg	34 to 51 lbs	40 mL
24 to 40 kg	52 to 88 lbs	50 mL
41 kg or more	89 lbs or more	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 5: 30 mL, 40 mL, 50 mL, or 60 mL) of compounded oral suspension (15 mg/mL). Refer to **Table 6**.

Table 6 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	29 mL	38.5 mL	48 mL	57 mL

Laboratories				

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 insure 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 7 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 7 Dosing Chart for Pharmacy-Compounded Suspension from TAMIFLU Capsules 75 mg

Body Weight (kg)	Body Weight (lbs)	Dose (mg)	Volume per Dose 15 mg/mL	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
15 kg or less	33 lbs or less	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 or more	89 lbs or more	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

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

Storage

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

TAMIFLU for Oral Suspension

Supplied as a white powder blend for constitution to a white tutti-frutti–flavored suspension. Available in glass bottles containing approximately 33 mL of suspension after constitution. Each bottle delivers 25 mL of suspension equivalent to 300 mg

oseltamivir base. Each bottle is supplied with a bottle adapter and 1 oral dispenser (NDC 0004-0810-95).

Storage

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

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

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