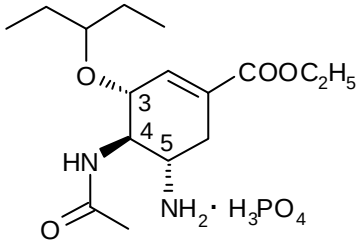
(oseltamivir phosphate)
CAPSULES

DESCRIPTION: TAMIFLU (oseltamivir phosphate) is available as a capsule containing 75-mg oseltamivir for oral use, in the form of oseltamivir phosphate. In addition to the active ingredient, each capsule contains pregelatinized starch, talc, povidone K 30, croscarmellose sodium, sodium stearyl fumarate, ethanol, and purified water. 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 #2 as the colorant. 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 via 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 (IC50 and IC90) 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.

Drug Resistance: Influenza A virus 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.

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In challenge studies of human subjects infected with influenza virus, 3% (3/102) of the post-treatment isolates showed emergence of influenza variants with decreased neuraminidase susceptibility to oseltamivir carboxylate. Genotypic analysis of these variants showed a specific mutation in the active site of neuraminidase compared to challenge virus.

In clinical studies of naturally acquired infection with influenza virus, 1.3% (4/301) of post-treatment isolates showed emergence of influenza variants with decreased neuraminidase susceptibility to oseltamivir carboxylate.

Genotypic analysis of these variants showed a specific mutation in the active site of neuraminidase compared to pretreatment isolates. The contribution of resistance due to alterations in the viral hemagglutinin has not been fully evaluated.

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, one of the three oseltamivir-induced mutations in the viral neuraminidase from clinical isolates is the same as one of the three mutations observed in zanamivir-resistant virus.

Insufficient information is available to fully characterize the risk of emergence of TAMIFLU resistance in clinical use.

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.

Influenza Challenge Studies: Antiviral activity of TAMIFLU was supported for influenza A and B by experimental challenge studies in volunteers who received intranasal inoculations of challenge strains of influenza virus. These subjects received TAMIFLU or placebo shortly after viral inoculation.

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 (Table 1).

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

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

Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily (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. Dose adjustment is recommended for patients with creatinine clearance below 30 mL/min. There are no data available in patients with renal failure (creatinine clearance <10 mL/min); therefore, caution is advised when administering the drug to those patients (see DOSAGE AND ADMINISTRATION: *Special Dosage Instructions*).

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 (see DOSAGE AND ADMINISTRATION: *Special Dosage Instructions*).

INDICATIONS AND USAGE: TAMIFLU is indicated for the treatment of uncomplicated acute illness due to influenza infection in adults who have been symptomatic for no more than 2 days. This indication is based on studies of naturally occurring influenza in which the predominant infection was influenza A, and influenza challenge studies in which antiviral activity of TAMIFLU was supported for influenza A and B (see *Description of Clinical Studies* and PRECAUTIONS).

Description of Clinical Studies: *Naturally Occurring Influenza Trials:* Two phase 3 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 these 849 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.

No increased efficacy was demonstrated in subjects receiving treatment of 150-mg TAMIFLU twice daily for 5 days.

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. Data on treatment of

influenza B are limited (see INDICATIONS AND USAGE: *Description of Clinical Studies*).

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

Efficacy of TAMIFLU in 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.

Use of TAMIFLU should not affect the evaluation of individuals for annual influenza vaccination in accordance with guidelines of the Center for Disease Controls and Prevention Advisory Committee on Immunization Practices. Efficacy of TAMIFLU has not been established for prophylactic use to prevent influenza.

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

Information for Patients: Patients should be instructed to begin treatment with TAMIFLU as soon as possible from the first appearance of flu symptoms.

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 shot. Patients should continue receiving an annual flu shot according to guidelines on immunization practices.

Drug Interactions: Information derived from pharmacology and pharmacokinetic studies of oseltamivir suggests that clinically significant drug interactions are unlikely.

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases, located predominantly in the liver. Drug interactions involving competition for esterases have not been extensively reported in literature. Low protein binding of oseltamivir and oseltamivir carboxylate suggests that the probability of drug displacement interactions is low.

In vitro studies demonstrate that neither oseltamivir nor oseltamivir carboxylate is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases.

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

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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.

Preliminary information shows that 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: Oseltamivir was found to be non-mutagenic in the Ames, human lymphocyte chromosome and mouse micronucleus tests. Oseltamivir carboxylate was also found to be non-mutagenic in the Ames and mouse lymphoma cell mutation tests.

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 to 24 h) of oseltamivir carboxylate.

Long-term carcinogenicity tests with oseltamivir have not been completed.

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 skeleton 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.

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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.

Pediatric Use: The safety and efficacy of TAMIFLU in children (<18 years) have not been established.

Geriatric Use: In an ongoing study of otherwise healthy elderly patients, >65 years (n=168), given the recommended dosing regimen of TAMIFLU, there was a reduction in the median time to improvement in the subjects receiving TAMIFLU similar to that seen in younger adults. No overall difference in safety was observed between these subjects and younger adults.

ADVERSE REACTIONS: A total of 1171 patients who participated in adult phase 3 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 3 treatment studies are shown in Table 2. 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.

Table 2. Adverse Events ³1% in the Treatment of Naturally Acquired Influenza With Dose of TAMIFLU 75 mg Twice Daily

	TAMIFLU 75 mg twice daily N=724		**Placebo N=716**	
Nausea (without vomiting)	72	(9.9%)	40	(5.6%)
Vomiting	68	(9.4%)	21	(2.9%)
Diarrhea	48	(6.6%)	70	(9.8%)
Bronchitis	17	(2.3%)	15	(2.1%)
Abdominal pain	16	(2.2%)	16	(2.2%)
Dizziness	15	(2.1%)	25	(3.5%)
Headache	13	(1.8%)	14	(2.0%)

Cough	9	(1.2%)	12	(1.7%)
Insomnia	8	(1.1%)	6	(0.8%)
Vertigo	7	(1.0%)	3	(0.4%)
Fatigue	7	(1.0%)	7	(1.0%)

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

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. A complete pack of ten capsules of TAMIFLU contains a total of 750 mg of oseltamivir.

DOSAGE AND ADMINISTRATION: ***Standard Dosage:*** The recommended oral dose of TAMIFLU is 75 mg twice daily for 5 days. Treatment should begin within 2 days of onset of symptoms of influenza. TAMIFLU may be taken with or without food (see *PHARMACOKINETICS*). However, when taken with food, tolerability may be enhanced in some patients.

Special Dosage Instructions: *Hepatic Impairment:* The safety and pharmacokinetics in patients with hepatic impairment have not been evaluated.

Renal Impairment: No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with a creatinine clearance of less than 30 mL/min, it is recommended that the dose be reduced to 75 mg of TAMIFLU once daily for 5 days. The drug has not been studied in patients with renal failure (creatinine clearance below 10 mL/min); therefore, caution is advised when administering the drug to those patient populations (see *PHARMACOKINETICS: Special Populations*).

Pediatric Patients: The safety and efficacy of TAMIFLU in children have not been established.

Geriatric Patients: No dose adjustment is required for geriatric patients (see *PHARMACOKINETICS: Special Populations* and PRECAUTIONS).

HOW SUPPLIED: TAMIFLU is 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 at 25ºC (77ºF); excursions permitted to 15º to 30ºC (59º to 86ºF). [See USP Controlled Room Temperature]

HLR 10/27/99

TAMIFLU™ (oseltamivir phosphate) CAPSULES

Manufactured by:

F. Hoffmann-La Roche Ltd.
Basel, Switzerland

Distributed by:

Pharmaceuticals

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

Licensor:

Gilead Sciences, Inc.
Foster City, California 94404

26684756-1099
25481675-1099

Issued: October 1999
Printed in USA

TAMIFLU™ (oseltamivir phosphate) CAPSULES

Roche

Patient Information About:

TAMIFLU™

(oseltamivir phosphate)
75 mg Capsules

This leaflet contains important patient information about TAMIFLU (oseltamivir phosphate), and should be read completely before beginning treatment. It does not, however, take the place of discussions with your doctor or health care professional about your medical condition or your treatment. This summary does not list all benefits and risks of TAMIFLU. The medication described here can only be prescribed and dispensed by a licensed health care professional, who has information about your medical condition and more information about the drug, including how to take it, what to expect, and potential side effects. If you have any questions about TAMIFLU talk with your doctor. Only your health care professional can determine if TAMIFLU is right for you.

What is TAMIFLU?

TAMIFLU (TAM-ih-floo) is a medicine to treat flu (infection caused by influenza virus). It belongs to a group of medicines called neuraminidase inhibitors. These medications attack the influenza virus and prevent it from spreading inside your body. TAMIFLU treats the cause of flu at its source, rather than simply masking symptoms. Each TAMIFLU capsule (grey/light-yellow) contains 75mg of active drug and should be taken by mouth.

Who should not take TAMIFLU?

You should not take TAMIFLU if you are allergic to oseltamivir phosphate or any other ingredients of TAMIFLU. Before starting treatment, make sure your doctor knows if you are taking any other medication or have any type of kidney disease.

Who should consider taking TAMIFLU?

Adult patients who have flu symptoms that appeared within the previous day or two. Typical symptoms of flu include sudden onset of fever, cough, headache, fatigue, muscular weakness, and sore throat.

What can I expect if I take TAMIFLU?

In two large clinical trials, one conducted in the USA and one conducted outside the USA, flu patients who took TAMIFLU recovered 1.3 days (30%) faster than flu patients who did not take TAMIFLU.

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Can I take other medications with TAMIFLU?

TAMIFLU has been shown to have a good safety profile, with minimal risk of drug interactions. Your doctor or health care professional may recommend taking over-the-counter medications to reduce fever or other symptoms while the antiviral action of TAMIFLU takes effect. Before starting treatment make sure that your health care professional knows if you are taking any other medication.

How and when should I take TAMIFLU?

TAMIFLU should be taken twice daily (once in the morning and once in the evening) for five days. TAMIFLU can be taken with food. As with many medicines, if taken with a light snack, milk, or a meal, the potential for stomach upset may be reduced. You should complete the entire treatment of ten capsules, even if you are feeling better. Never share TAMIFLU with anyone, even if they have the same symptoms.

It is important that you begin your treatment with TAMIFLU as soon as possible from the first appearance of your flu symptoms.

What if I miss a dose?

If you forget to take your medicine at any time, take the missed dose as soon as you remember, except if it is near the next dose (within 2 hours). Then continue to take TAMIFLU at the usual times. You do not need to take a double-dose. If you have missed several doses, inform your doctor and follow the advice given to you.

What are common possible side effects of TAMIFLU treatment?

TAMIFLU is generally well tolerated. The most common side effects are nausea and vomiting. Taking TAMIFLU with food may reduce the potential of these side effects. If you notice any side effects not mentioned in this leaflet or if you have any concerns about the side effects you are experiencing, please inform your health care professional.

Should I get a flu shot?

TAMIFLU is not a substitute for a flu shot. You should continue receiving an annual flu shot according to guidelines on immunization practices that your physician can discuss with you.

What if I am pregnant or nursing?

If you are pregnant or planning to become pregnant while taking TAMIFLU, talk to your doctor before taking this medication. TAMIFLU is normally not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.

TAMIFLU™ (oseltamivir phosphate) CAPSULES

How and where should I store TAMIFLU?

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

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