Tamiflu®
oseltamivir phosphate

CAPSULES AND FOR ORAL SUSPENSION

Before prescribing, please see complete product information, a summary of which follows:

INDICATIONS AND USAGE:

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

Prophylaxis of Influenza: TAMIFLU is indicated for the prophylaxis of influenza in adult patients and adolescents 13 years 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.

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.

Information for Patients: Patients should be instructed to begin treatment with TAMIFLU as soon as possible from the first appearance of flu symptoms. Similarly, prevention should begin as soon as possible after exposure, at the recommendation of a physician.

Patients should be instructed to take any missed doses as soon as they remember, except if it is near the next scheduled dose (within 2 hours), and then continue to take TAMIFLU at the usual times.

TAMIFLU is not a substitute for a flu vaccination. Patients should continue receiving an annual flu vaccination according to guidelines on immunization practices.

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

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

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

Cimetidine, a nonspecific 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.

Pediatric Use: The safety and efficacy of TAMIFLU in pediatric patients younger than 1 year of age have not been established.

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. 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.

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 1. 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 1. Most Frequent Adverse Events in Studies in Naturally Acquired Influenza

	Treatment		Prophylaxis	
Adverse Event	**Placebo N=716**	**Oseltamivir 75 mg bid N=724**	**Placebo N=1434**	**Oseltamivir 75 mg qd N=1480**
Nausea (without vomiting)	40 (5.6%)	72 (9.9%)	56 (3.9%)	104 (7.0%)
Vomiting	21 (2.9%)	68 (9.4%)	15 (1.0%)	31 (2.1%)
Diarrhea	70 (9.8%)	48 (6.6%)	38 (2.6%)	48 (3.2%)
Bronchitis	15 (2.1%)	17 (2.3%)	17 (1.2%)	11 (0.7%)
Abdominal pain	16 (2.2%)	16 (2.2%)	23 (1.6%)	30 (2.0%)
Dizziness	25 (3.5%)	15 (2.1%)	21 (1.5%)	24 (1.6%)
Headache	14 (2.0%)	13 (1.8%)	251 (17.5%)	298 (20.1%)
Cough	12 (1.7%)	9 (1.2%)	86 (6.0%)	83 (5.6%)
Insomnia	6 (0.8%)	8 (1.1%)	14 (1.0%)	18 (1.2%)
Vertigo	4 (0.6%)	7 (1.0%)	3 (0.2%)	4 (0.3%)
Fatigue	7 (1.0%)	7 (1.0%)	107 (7.5%)	117 (7.9%)

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.

Prophylaxis Studies: A total of 3434 subjects (adolescents, healthy adults and elderly) participated in phase III prophylaxis studies, of whom 1480 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 (Table 1). 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.

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 2. 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.

Table 2. Adverse Events Occurring On Treatment in >1% of Pediatric Patients Enrolled in Phase III Trials of TAMIFLU Treatment of Naturally Acquired Influenza

Adverse Event	Placebo N=517	TAMIFLU 2 mg/kg twice daily N=515
Vomiting	48 (9.3%)	77 (15.0%)
Diarrhea	55 (10.6%)	49 (9.5%)
Otitis media	58 (11.2%)	45 (8.7%)
Abdominal pain	20 (3.9%)	24 (4.7%)
Asthma (including aggravated)	19 (3.7%)	18 (3.5%)
Nausea	22 (4.3%)	17 (3.3%)
Epistaxis	13 (2.5%)	16 (3.1%)
Pneumonia	17 (3.3%)	10 (1.9%)
Ear disorder	6 (1.2%)	9 (1.7%)
Sinusitis	13 (2.5%)	9 (1.7%)
Bronchitis	11 (2.1%)	8 (1.6%)
Conjunctivitis	2 (0.4%)	5 (1.0%)
Dermatitis	10 (1.9%)	5 (1.0%)
Lymphadenopathy	8 (1.5%)	5 (1.0%)
Tympanic membrane disorder	6 (1.2%)	5 (1.0%)

Observed During Clinical Practice for Treatment: 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.

General: Rash, swelling of the face or tongue, toxic epidermal necrolysis

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.

Pediatric Patients: The safety and efficacy of TAMIFLU for prophylaxis in pediatric patients younger than 13 years of age have not been established. The safety and efficacy of TAMIFLU for treatment in pediatric patients younger than 1 year of age have not been established.

Geriatric Patients: No dose adjustment is required for geriatric patients.

Preparation of Oral Suspension:

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

Manufactured by: F. Hoffmann-La Roche Ltd., Basel, Switzerland

Distributed by:

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