PRODUCT MONOGRAPH

PR TAMIFLU®

oseltamivir phosphate capsule

30 mg, 45 mg and 75 mg oseltamivir

oseltamivir phosphate powder for oral suspension

12 mg/mL oseltamivir when reconstituted

Antiviral Agent

Hoffmann-La Roche Limited
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PR TAMIFLU®

Oseltamivir phosphate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsule / 30 mg, 45 mg and 75 mg oseltamivir	None *For a complete listing see Dosage Forms, Composition and Packaging section.*
Oral	Powder for Oral Suspension / 12 mg/mL oseltamivir when reconstituted	Sorbitol (see WARNINGS AND PRECAUTIONS) *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Treatment of Influenza

TAMIFLU (oseltamivir phosphate) is indicated for:

- The treatment of uncomplicated acute illness due to influenza infection in adults and adolescents (>13 years) who have been symptomatic for no more than 2 days.

  The treatment indication is based on two Phase III clinical studies of naturally occurring influenza in adults in which the predominant infection was influenza A (95%) and a limited number with influenza B (3%) and influenza of unknown type (2%), reflecting the distribution of these strains in the community. The indication is also supported by influenza A and B challenge studies. No data are available to support the safety and efficacy of TAMIFLU in adult patients who commenced treatment after 40 hours of onset of symptoms.

- The treatment of uncomplicated acute illness due to influenza in pediatric patients 1 year and older who have been symptomatic for no more than 2 days.

  The pediatric indication is based on one Phase III clinical study of naturally occurring influenza in pediatric patients aged 1 to 12 years in which 67% of influenza infected patients were infected with influenza A and 33% with influenza B.

TAMIFLU, when taken as recommended for the treatment of influenza, alleviates the symptoms and reduces their duration, (see CLINICAL TRIALS).

Prevention/Prophylaxis of Influenza

The decision to administer TAMIFLU for prophylaxis to close contacts should be based on the knowledge that influenza is circulating in the area and the index case demonstrates characteristic symptoms of influenza. TAMIFLU is not effective in providing prophylaxis for respiratory infections other than influenza therefore a proper diagnosis of the index case is important.

TAMIFLU is not a substitute for influenza vaccination. Vaccination is the preferred method of prophylactic prevention against influenza. The use of TAMIFLU should not affect the evaluation of individuals for annual influenza vaccination, in accordance to "Health Canada. An Advisory Committee Statement on Influenza Vaccination for the Current Year/Season."

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations taking into consideration variability of epidemiology and the impact of the disease in different geographical areas and patient populations.

TAMIFLU is indicated for:

- The prevention of influenza illness in adults and adolescents 13 years and older following close contact with an infected individual (the index case).

  The prevention indication is based on a phase III clinical study programme consisting of 4 Phase III clinical trials.

- The prevention of influenza illness in pediatric patients 1 year and older following close contact with an infected individual (the index case).

  This indication is based on a substudy of pediatric patients in a Phase III clinical trial.

CONTRAINDICATIONS

- TAMIFLU (oseltamivir phosphate) is contraindicated in patients with known hypersensitivity to any of the components of the product. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

No increased efficacy was demonstrated in adult subjects receiving 150 mg TAMIFLU (oseltamivir phosphate) twice daily for 5 days compared to those receiving 75 mg twice daily for the treatment of influenza.

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.

Efficacy of TAMIFLU in patients who begin treatment after 48 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 prevention courses have not been studied.

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

Endocrine and Metabolism

A bottle of 30 g TAMIFLU powder for oral suspension contains 25.713 g of sorbitol. One dose of 45 mg oseltamivir administered twice daily delivers 2.6 g of sorbitol which is unsuitable for subjects with hereditary fructose intolerance.

Hepatic

There have been post-marketing reports of elevated liver enzymes and hepatotoxicity including fulminant hepatits/hepatic failure, in some cases with fatal outcome, where a causal relationship with oseltamivir could not be excluded, especially in patients with pre-existing liver disease.

The safety, efficacy and pharmacokinetics of oseltamivir in patients with severe hepatic impairment have not been studied (see DOSAGE AND ADMINISTRATION: Dosage Adjustment, Hepatic Impairment).

Neuropsychiatric

There have been post-marketing reports (mostly from Japan) of delirium and self-injury, in some cases resulting in fatal outcomes, in patients with influenza who were receiving TAMIFLU. Because these events were reported voluntarily during clinical practice, estimate of frequency cannot be made but they appear to be uncommon based on TAMIFLU usage data. These events were reported primarily among pediatric patients. The contribution of TAMIFLU to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behaviour. If neuropsychiatric symptoms occur, the risks and benefits of continuing

treatment should be evaluated for each patient (see ADVERSE REACTIONS: Post-Market Adverse Drug Reactions, Neurologic, Psychiatric).

Influenza can be associated with a variety of neurologic and behavioural symptoms which can include events such as hallucinations, delirium, and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

Renal

Renal Impairment: No dosing recommendation is available for patients undergoing routine hemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤ 10 mL/min (see ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION: Dosage Adjustment).

Resistance

In clinical studies of naturally acquired infection, the cumulative incidence of oseltamivir-resistant virus by phenotyping alone or by phenotyping and genotyping was 0.32% (4/1245) or 0.4% (5/1245) respectively in adult/adolescent patients. In children with naturally acquired influenza virus infection, resistance was determined in 6 clinical studies WV15731 (0%; 0/5), WV15758 (8%; 15/183), WV15759/WV15871 (0%, 0/60), JV16284 (19%, 8/43), WV16193 (0%, 0/147), NV16871 (8%, 2/26). From the data obtained in these studies, the cumulative incidence of oseltamivir resistance in pediatric patients aged 1 to 12 years was 4.1% (19/464) based on phenotyping and 5.4% (25/464) based on phenotyping and genotyping (full genotyping was not performed on all patients). The patients cleared the virus normally and showed no clinical deterioration.

There has been no evidence for emergence of drug resistance associated with the use of TAMIFLU in clinical studies conducted to date in post-exposure (7 days), post-exposure within the household groups (10 days) and seasonal (42 days) prophylaxis of influenza (see MICROBIOLOGY: Resistance).

Insufficient information is available to fully characterize the risk of emergence of resistance to TAMIFLU in clinical use. (see MICROBIOLOGY: Resistance).

Skin and Hypersensitivity Reactions

Severe skin and hypersensitivity reactions have been reported since marketing in patients treated with TAMIFLU (see Post-Market Adverse Reactions).

Special Populations

Pregnant Women: At present, insufficient data are available in pregnant women taking TAMIFLU to enable an evaluation of the potential for TAMIFLU to cause fetal malformations or fetal toxicity. TAMIFLU should therefore be used during pregnancy only if the potential benefit justifies the potential risk to the 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. An increased incidence of abortion was seen in the 500 mg/kg/day group. There was a dose-dependent increase in the incidence rates of a variety of minor skeletal individual 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. In view of the isolated nature of this finding it was considered to be of doubtful toxicological significance. For the results of administration of oseltamivir to juvenile rats see WARNINGS AND PRECAUTIONS, Nursing Women.

Nursing Women*:* It is not known whether oseltamivir or the active metabolite are excreted in human milk. In lactating rats, oseltamivir and the active metabolite are excreted in the milk. TAMIFLU should not be used by mothers who are nursing children under one year of age due to the potential risk to the nursing infant. Administration of oseltamivir to juvenile rats resulted in a high mortality rate (see TOXICOLOGY: Multiple Dose Toxicity).

Pediatrics (< *1* year of age): TAMIFLU should not be used in children under 1 year of age (see TOXICOLOGY: Multiple Dose Toxicity). The safety and efficacy of TAMIFLU in infants younger than 1 year of age have not been established (see CLINICAL TRIALS).

Geriatrics (≥ *65* years of age): Efficacy of TAMIFLU in the treatment of elderly patients has not been evaluated. Safety data in 372 elderly patients (≥65 years old) showed no overall difference between these subjects and younger adults. Based on drug exposure and tolerability, dosage adjustments are not anticipated for elderly patients (see ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Geriatrics).

Safety has been demonstrated in elderly residents of nursing homes who took TAMIFLU for the prevention of influenza. Many of these individuals had cardiac and/or respiratory disease, and most had received vaccine that season (see CLINICAL TRIALS).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In adult treatment studies with TAMIFLU (oseltamivir phosphate) the most frequently reported adverse events were nausea and vomiting. In the prevention studies adverse events were qualitatively very similar to those seen in the treatment studies. In the pediatric treatment and prophylaxis studies the most frequently reported adverse event was vomiting.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adult Treatment Studies

In a total of 2107 patients, including patients on placebo and 75 mg b.i.d. TAMIFLU, in adult phase III studies in the treatment of influenza, the most frequently reported adverse events were nausea and vomiting. These events were transient and generally occurred with first dosing. These events did not lead to patient discontinuation of study drug in the vast majority of instances. At the recommended dose of 75 mg twice daily, three patients withdrew because of nausea and the same number withdrew because of vomiting.

In adult phase III treatment studies, some adverse events occurred more frequently in patients taking TAMIFLU compared to those taking placebos. The adverse events that occurred the most frequently at the recommended dose, either for treatment or prophylaxis, are shown in Table 1. This summary includes healthy young adults and "at risk" patients (patients at higher risk of developing complications associated with influenza e.g. elderly patients and patients with chronic cardiac or respiratory disease). Those events with an incidence of ≥ 1% and which were reported more frequently in patients taking TAMIFLU compared with placebo, irrespective of causality, were nausea, vomiting, abdominal pain and headache.

Table 1: Most Frequent Adverse Events in Studies in Naturally Acquired Influenza

Adverse Event System Organ Class (MedDRA)	Treatment*				Prevention			
	TAMIFLU 75 mg twice daily for 5 days N=1057		Placebo N=1050		TAMIFLU 75 mg once daily N=1480		Placebo N=1434	
Ear and Labyrinth Disorders								
Vertigo**	9	(0.9%)	6	(0.6%)	4	(0.3%)	3	(0.2%)
Gastrointestinal Disorders								
Nausea (without vomiting)	113	(10.7%)	71	(6.8%)	104	(7.0%)	56	(3.9%)
Vomiting	85	(8.0%)	32	(3.0%)	31	(2.1%)	15	(1.0%)
Diarrhea	58	(5.5%)	84	(8.0%)	48	(3.2%)	38	(2.6%)
Abdominal pain	23	(2.2%)	21	(2.0%)	30	(2.0%)	23	(1.6%)
General Disorders and Administration Site								

Adverse Event System Organ Class (MedDRA)	Treatment*				Prevention			
	TAMIFLU 75 mg twice daily for 5 days N=1057		Placebo N=1050		TAMIFLU 75 mg once daily N=1480		Placebo N=1434	
Reactions								
Fatigue**	8	(0.8%)	7	(0.7%)	117	(7.9%)	107	(7.5%)
Infections and Infestations								
Bronchitis	39	(3.7%)	52	(5.0%)	11	(0.7%)	17	(1.2%)
Nervous System Disorders								
Dizziness	20	(1.9%)	31	(3.0%)	24	(1.6%)	21	(1.5%)
Headache	17	(1.6%)	16	(1.5%)	298	(20.1%)	251	(17.5%)
Insomnia	11	(1.0%)	10	(1.0%)	18	(1.2%)	14	(1.0%)
Respiratory, Thoracic and Mediastinal Disorders								
Cough**	10	(0.9%)	12	(1.1%)	83	(5.6%)	86	(6.0%)

* Adverse events included are all events reported the most frequently in the treatment studies in the oseltamivir 75 mg bid. Group, and events are ordered by decreasing incidence in that group.

** These events no longer qualify as among the most-frequently recorded events for the treatment group but are included here for completeness as they were included in a previous version of this table which was based on a smaller dataset.

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.

Adult Prevention Studies

A total of 3434 subjects (adolescents, healthy adults and elderly) participated in 3 phase III prevention studies, of whom 1480 received the recommended dose of 75 mg once daily. Adverse events were qualitatively very similar to those seen in the treatment studies (see Table 1). Additional adverse events ≥1% in the prevention studies included 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.

In a fourth study, an additional 399 subjects received 75 mg of TAMIFLU once daily for 10 days following the identification of a household index case. Similar to previous studies, nausea (8.3%), vomiting (4.5%), diarrhea (0.8%) and headache (7.8%) were among the most commonly reported adverse events.

Pediatric Treatment Studies
A total of 1032 pediatric patients aged 1 to 12 years (including 698 otherwise healthy pediatric patients aged 1 to 12 and 334 asthmatic pediatric patients aged 6 to 12) 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 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.

Although otitis media, pneumonia, sinusitis and bronchitis were all reported in >1% of pediatric patients receiving TAMIFLU, the incidence of these events in the group treated with TAMIFLU was lower than that in the placebo treated group.

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

Table 2: Most Frequent Adverse Events Occurring in Children Aged 1 to 12 Years in Studies in Naturally Acquired Influenza

	Treatment[a]				Treatment[b]		Prophylaxis[b]	
Adverse Events **System Organ Class (MedDRA)**	**TAMIFLU 2 mg/kg twice daily N= 515**		**Placebo N= 517**		**TAMIFLU Unit Dose[c] N=158**		**TAMIFLU Unit Dose[c] N=99**	
Blood and Lymphatic system Disorders								
Lymphadenopathy	5	(1.0%)	8	(1.5%)	1	(0.6%)	-	
Ear and Labyrinth Disorders								
Ear disorder	9	(1.7%)	6	(1.2%)	-		-	
Tympanic membrane disorder	5	(1.0%)	6	(1.2%)	-		-	
Eye Disorders								
Conjuctivitis	5	(1.0%)	2	(0.4%)	-		-	
Gastrointestinal Disorders								
Vomiting	77	(15.0%)	48	(9.3%)	31	(19.6%)	10	(10.1%)
Diarrhea	49	(9.5%)	55	(10.6%)	5	(3.2%)	1	(1.0%)
Abdominal pain	24	(4.7%)	20	(3.9%)	3	(1.9%)	3	(3.0%)
Nausea	17	(3.3%)	22	(4.3%)	10	(6.3%)	4	(4.0%)
Infections and Infestations								
Otitis media	45	(8.7%)	58	(11.2%)	2	(1.3%)	2	(2.0%)
Pneumonia	10	(1.9%)	17	(3.3%)	-		-	
Sinusitis	9	(1.7%)	13	(2.5%)	-		-	
Bronchitis	8	(1.6%)	11	(2.1%)	3	(1.9%)	-	
Respiratory, Thoracic and Mediastinal Disorders								
Asthma (including aggravated)	18	(3.5%)	19	(3.7%)	-		1	(1.0%)
Epistaxis	16	(3.1%)	13	(2.5%)	2	(1.3%)	1	(1.0%)
Skin and Subcutaneous Tissue Disorders								
Dermatitis	5	(1.0%)	10	(1.9%)	1	(0.6%)	-	

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

[b] Uncontrolled study comparing treatment (twice-daily dosing for 5 days) with prophylaxis (once-daily dosing for 10 days).

[c] Unit dose = age-based dosing (see DOSAGE AND ADMINISTRATION).

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

Pediatric Prevention Studies
Pediatric patients aged 1 to 12 years participated in a post-exposure prophylaxis study in households, both as index cases (n=134) and as contacts (n=222). Gastrointestinal events were the most frequent, particularly vomiting. TAMIFLU was well tolerated in this study, the adverse events noted being consistent with those previously observed (see Table 2).

Post-Market Adverse Drug Reactions
The following adverse reactions have been identified during post-marketing 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.

Skin and hypersensitivity reactions: dermatitis, rash, eczema, urticaria, erythema multiforme, Stevens-Johnson-Syndrome, toxic epidermal necrolysis, anaphylactic/anaphylactoid reactions and face edema

Liver and biliary system: elevated liver enzymes, hepatotoxicity including fulminant hepatitis/hepatic failure, in some cases with fatal outcome

Gastro-intestinal disorders: gastro-intestinal bleeding, hemorrhagic colitis

Neurologic: seizure

Psychiatric: delirium, including symptoms such as altered level of consciousness, confusion, abnormal behavior leading to self-injury, delusions, hallucinations, agitation, anxiety, nightmares (see WARNINGS AND PRECAUTIONS).

DRUG INTERACTIONS

Overview
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 demonstrated that neither oseltamivir nor the active metabolite are good substrates for P450 mixed-function oxidases or for glucuronyl transferases.

Drug-Drug Interactions
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 its active metabolite.

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 the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion

capacity of these pathways. Co-administration of probenecid results in an approximate two-fold increase in exposure to the active metabolite due to a decrease in active anionic tubular secretion in the kidney. However, due to the wide safety margin of the active metabolite, no dose adjustments are required when co-administering with probenecid. Other drugs excreted via anionic tubular secretion have not been evaluated.

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

In six subjects, co-administration with acetaminophen did not alter plasma levels of oseltamivir, its active metabolite, or acetaminophen.

Co-administration with paracetamol does not alter plasma levels of oseltamivir, its active metabolite, or paracetamol.

No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetyl-salicylic acid, cimetidine or with antacids (Magnesium and aluminum hydroxides and calcium carbonates).

In phase III treatment and prophylaxis clinical studies, TAMIFLU (oseltamivir phosphate) has been administered with commonly used drugs such as ACE inhibitors (enalapril, captopril), thiazide diuretics (bendrofluazide), antibiotics (penicillin), H_2-receptor blockers (cimetidine), and analgesic agents (acetylsalicylic acid, ibuprofen and paracetamol). No change in adverse event profile or frequency has been observed as a result of co-administration of TAMIFLU with these compounds.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbs have not been established.

Drug-Laboratory Tests
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Hepatic Impairment: The safety, efficacy and pharmacokinetics in patients with severe hepatic impairment have not been studied. No studies have been carried out in pediatric patients with hepatic impairment.

Infants: The safety and efficacy of TAMIFLU (oseltamivir phosphate) in infants younger than 1 year of age have not been established. TAMIFLU should not be used in children under 1 year of age (see TOXICOLOGY: Multiple Dose Toxicity).

For information on renal impairment and elderly patients see Dosage Adjustment section.

Recommended Dose – Treatment of Influenza
Treatment should begin no more than two days after the onset of symptoms of influenza.

Adults and Adolescents (≥ 13 years): The recommended oral dose of TAMIFLU capsules for the treatment of influenza in adults and adolescents 13 years and older is 75 mg twice daily, for 5 days.

Pediatrics (1 to 12 years): The recommended oral dose of TAMIFLU oral suspension for pediatric patients 1 year and older is shown in the table below. TAMIFLU oral suspension may also be used by adult patients who cannot swallow a capsule. If TAMIFLU oral suspension is not available, TAMIFLU capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup. For children old enough to safely swallow capsules, the 30 and 45 mg capsules can also be taken as outlined in the table below.

Body Weight in kg	Body Weight in lbs	Recommended Dose for 5 Days
≤15 kg	≤ 33 lbs	30 mg twice daily
> 15 kg to 23 kg	> 33 lbs to 51 lbs	45 mg twice daily
> 23 kg to 40 kg	> 51 lbs to 88 lbs	60 mg twice daily
> 40 kg	> 88 lbs	75 mg twice daily

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.

Recommended Dose – Prevention of Influenza
Therapy should begin within 2 days of exposure after the onset of symptoms in the index case and continue for at least ten days. Viral shedding may continue for up to 14 days in children and elderly after the onset of influenza illness. Therefore, if the index case is a child or an elderly person, therapy with TAMIFLU for prevention may continue for up to 14 days.

Patients should be instructed to complete the entire course of therapy.

Adults and adolescents (≥ 13 years): The recommended oral dose of TAMIFLU for prevention of influenza following close contact with an infected individual (the index case) is 75 mg once daily.

Pediatrics (1 to 12 years): The recommended dose of TAMIFLU oral suspension for prevention in pediatric patients 1 year and older is shown in the table below. TAMIFLU oral suspension may also be used by adult patients who cannot swallow a capsule. If TAMIFLU oral suspension is not available, TAMIFLU capsules may be opened and mixed with sweetened liquids such as regular or sugar-free chocolate syrup. For children old enough to safely swallow capsules, the 30 and 45 mg capsules can also be taken as outlined in the table below.

Body Weight in kg	Body Weight in lbs	Recommended Dose for at least 10 Days
≤15 kg	≤ 33 lbs	30 mg once daily
> 15 kg to 23 kg	> 33 lbs to 51 lbs	45 mg once daily
> 23 kg to 40 kg	> 51 lbs to 88 lbs	60 mg once daily
> 40 kg	> 88 lbs	75 mg once daily

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.

Dosage Adjustment

Hepatic Impairment: No dose adjustment is required in adult patients with mild or moderate hepatic impairment (See ACTIONS AND CLINICAL, PHARMACOLOGY: Special Populations and Conditions, Hepatic Impairment).

Renal Impairment: No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min.

No dosing recommendation is available for patients undergoing routine hemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤ 10 mL/min (see ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions, Renal Impairment).

Treatment of Influenza: In patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose be reduced to 75 mg of TAMIFLU once daily for 5 days.

Prevention of influenza: In patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose be reduced to 75 mg of TAMIFLU every other day, or alternatively, one 30 mg capsule or 30 mg suspension once daily.

Elderly Patients: No dose adjustment is required for elderly patients (See WARNINGS AND PRECAUTIONS: Special Populations, Geriatrics).

Missed Dose
The missed dose should be taken as soon as remembered, then the regular dosing schedule should be continued. Two doses of TAMIFLU should not be taken at the same time.

Administration
TAMIFLU may be taken with or without food (see ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics, Absorption). However, taking with food may enhance tolerability in some patients.

Reconstitution of Oral Suspension:

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

1. Tap the closed bottle several times to loosen the powder.
2. Measure 52 mL of water in a graduated cylinder.
3. Add the total amount of water for reconstitution to the bottle and shake the closed bottle well for 15 seconds.
4. Remove the child-resistant cap and push bottle adapter into neck of 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.

Dispense with patient information leaflet and oral dispenser. It is recommended to write the date of expiration of the reconstituted suspension on the bottle label. (The shelf life of the reconstituted suspension is 10 days if stored at room temperature (not above 25°C) or 17 days if stored in a refrigerator (2°C - 8°C)).

A bottle of 30 g TAMIFLU powder for oral suspension contains 25.713 g of sorbitol. One dose of 45 mg oseltamivir administered twice daily delivers 2.6 g of sorbitol which is unsuitable for subjects with hereditary fructose intolerance (see WARNINGS AND PRECAUTIONS: Endocrine and Metabolism).

Note: Shake the TAMIFLU oral suspension well before each use.

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 Health Canada-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 the vehicle 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 Health Canada-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 3.

Table 3: 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 (Ora-Sweet SF) that are needed to prepare the Total Volume (calculated from Table 3: 30 mL, 40 mL, 50 mL, or 60 mL) of compounded oral suspension (15 mg/mL). Refer to Table 4.

Table 4: Number of TAMIFLU 75 mg Capsules and Amount of Vehicle (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 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 vehicle. The suspension is caused by some of the inert ingredients of TAMIFLU Capsules which are insoluble in the vehicle.)
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.]
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:

Compounded with Ora-Sweet®SF: Stable for 5 weeks (35 days) when stored at 25°C.

Note: The storage conditions are based on stability studies of compounded oral suspensions, using the above mentioned vehicle, 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 Provincial and Federal Pharmacy Regulations. **Refer to Table 5 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 5: 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	≤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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TAMIFLU (oseltamivir phosphate) is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active metabolite, oseltamivir carboxylate. The active metabolite is a selective inhibitor of influenza A and B virus neuraminidase enzymes which are glycoproteins found on the virion surface. Viral neuraminidase is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells and the further spread of infectious virus in the body. 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.

Oseltamivir is readily absorbed after oral administration and converted by hepatic esterases to its active metabolite. The mean volume of distribution (V_{ss}) of the active metabolite is approximately 23 L. The active metabolite is not further metabolized and is eliminated in the urine. The half-life of elimination of this metabolite is 6 to 10 hours. Renal clearance (18.8 L/h) exceeds glomerular filtration rate (7.5 L/h), indicating that tubular secretion in addition to glomerular filtration occurs. The prodrug which reaches the systemic circulation (less than 5%) is eliminated by renal excretion also. The binding of oseltamivir to human plasma protein is 42% and that of the active metabolite is negligible, approximately 3%.

Exposure to the active metabolite is inversely proportional to declining renal function.

Pharmacokinetics

Absorption: Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of TAMIFLU and is extensively converted predominantly by hepatic esterases to the active metabolite. At least 75% of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the prodrug is less than 5% relative to the active metabolite. Plasma concentrations of active metabolite are proportional to dose and are not significantly affected by co-administration with food (see DOSAGE AND ADMINISTRATION).

Distribution*:* The mean volume of distribution (V_{SS}) of the active metabolite is approximately 23 litres in humans.

The binding of oseltamivir to human plasma protein is 42% and that of the active metabolite is negligible, approximately 3%.

Metabolism*:* Oseltamivir is extensively converted to the active metabolite by esterases located predominantly in the liver. Neither oseltamivir nor the active metabolite are substrates for, or inhibitors of, cytochrome P450 isoforms.

Excretion: Absorbed oseltamivir is primarily (>90%) eliminated by conversion to the active metabolite. The active metabolite is not further metabolized and is eliminated in the urine. Peak plasma concentrations of the active metabolite decline with a half-life of 6 to 10 hours in most subjects. The active drug 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 in addition to glomerular filtration occurs. Less than 20% of an oral radiolabelled dose is eliminated in feces.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of oseltamivir have been evaluated in single dose pharmacokinetic studies in pediatric patients aged 1 to 16 years. Multiple dose pharmacokinetics were studied in a small number of pediatric patients aged 3-12 years enrolled in a clinical trial. Younger pediatric patients cleared both the prodrug and the active metabolite faster than adults resulting in lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg capsule dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in pediatric patients over 12 years of age are similar to those in adults.

TAMIFLU should not be used in children under 1 year of age (see TOXICOLOGY: Multiple Dose Toxicity).

Geriatrics: Exposure to the active metabolite at steady-state was 25% to 35% higher in elderly patients (age range 65 to 78) compared to young adults given comparable doses of TAMIFLU. Half-lives observed in the elderly patients were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for elderly patients for either treatment or prevention (see DOSAGE AND ADMINISTRATION: Dosage Adjustment).

Hepatic Impairment: The safety, efficacy and pharmacokinetics of TAMIFLU in patients with severe hepatic impairment have not been studied (See WARNINGS AND PRECAUTIONS: Hepatic). In a clinical study of adult patients with moderate hepatic impairment (N=11), compared with healthy volunteers (N=23), metabolic conversion of oseltamivir into the active metabolite oseltamivir carboxylate was not significantly altered (See DOSAGE AND ADMINISTRATION: Dosage Adjustment, Hepatic Impairment). No studies have been carried out in pediatric patients with hepatic impairment.

Renal Impairment: Administration of 100 mg of TAMIFLU twice daily for five days to patients with various degrees of renal impairment showed that exposure to the active metabolite is inversely proportional to declining renal function.

No dosing recommendation is available for patients undergoing routine hemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤ 10 mL/min.

Treatment of Influenza: In patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose be reduced to 75 mg of TAMIFLU once daily for 5 days.

Prevention of influenza: In patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose be reduced to 75 mg of TAMIFLU every other day, or alternatively, one 30 mg capsule or 30 mg suspension every day (See DOSAGE AND ADMINISTRATION: Dosage Adjustment, Renal Impairment).

STORAGE AND STABILITY

TAMIFLU (oseltamivir phosphate) Capsules: Store at 15 to 25°C.

TAMIFLU Powder for Oral Suspension: Store dry powder at 15 to 25ºC. Store reconstituted suspension:
a) at room temperature (not above 25°C). Discard unused portion within 10 days of reconstitution.
or
b) in a refrigerator (2°C - 8°C). Discard unused portion within 17 days of reconstitution.
Do not freeze reconstituted suspension.

TAMIFLU Pharmacy-Compounded Suspension: Store reconstituted suspension:
(a) compounded with Ora-Sweet®SF: Stable for 5 weeks (35 days) when stored at 25°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TAMIFLU (oseltamivir phosphate) 30 mg, 45 mg and 75 mg Capsules

Composition

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. In addition to the active ingredient, each capsule contains corn starch, croscarmellose sodium, povidone K30, sodium stearyl fumarate and talc. The 30 mg capsule shell contains gelatin, red iron oxide, yellow iron oxide and titanium dioxide. The 45 mg capsule shell contains gelatin, black iron oxide and titanium dioxide. The 75 mg capsule shell contains gelatin, black iron oxide, red iron oxide, yellow iron oxide and titanium dioxide. Each capsule is printed with blue ink, which includes FD&C Blue No. 2 as a colorant.

Availability
TAMIFLU 30 mg capsules are available as 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.

TAMIFLU 45 mg capsules are available as 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.

TAMIFLU 75 mg capsules are available as 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.

All three capsules strengths are available in blister packages of 10.

TAMIFLU Powder for Oral Suspension
Composition
TAMIFLU powder for oral suspension contains 900 mg oseltamivir as oseltamivir phosphate per bottle, which when reconstituted contains 12 mg/mL oseltamivir. The nonmedicinal ingredients are: monosodium citrate, saccharin sodium, sodium benzoate, sorbitol, titanium dioxide, tutti-frutti flavoring and xanthan gum.

Availability
TAMIFLU powder for oral suspension is available as a white powder blend for reconstitution to a white tutti-frutti-flavored suspension. Available in 100 mL glass bottles with a bottle adapter and 1 oral dispenser *. Net contents after reconstitution: 75 mL containing oseltamivir phosphate equivalent to 900 mg oseltamivir base.

*Oral dosing dispenser manufactured by F. Hoffmann-La Roche Ltd., 4070 Basel, Switzerland.