

Data Sheet

Tamiflu[®]

Oseltamivir 30 mg, 45 mg and 75 mg capsules; 12 mg/mL powder for oral suspension

Antiviral

Pharmaceutical Form

Hard capsule - 30 mg, 45 mg and 75 mg; Powder for oral suspension - 12 mg/mL.

Qualitative and Quantitative Composition

Active ingredient

Oseltamivir phosphate.

30 mg capsules contain 39.4 mg oseltamivir phosphate equivalent to 30 mg of oseltamivir.

45 mg capsules contain 59.1 mg oseltamivir phosphate equivalent to 45 mg of oseltamivir.

75 mg capsules contain 98.5 mg oseltamivir phosphate equivalent to 75 mg of oseltamivir.

Powder for oral suspension contains 1.182 g oseltamivir phosphate, which when reconstituted with 52 mL of water makes 75 mL of 12 mg/mL oseltamivir.

Excipients

Capsules

Capsule fill: Povidone K30, pre-gelatinised starch, croscarmellose sodium, talc, sodium stearyl fumarate.

Capsule shell: Black iron oxide, red iron oxide, yellow iron oxide, titanium dioxide, gelatin.

Printing ink: Dehydrated alcohol, shellac, n-butyl alcohol, titanium dioxide, FDC Blue 2, SDA-3A alcohol.

Powder for oral suspension

Sorbitol, titanium dioxide, sodium benzoate, xanthan gum, sodium dihydrogen citrate (monosodium citrate), saccharin sodium, flavour – PERMASEAL 11900-31 Tutti Frutti.

Appearance

Capsules:

30 mg hard gelatin capsule consists of a light yellow opaque body bearing the imprint "ROCHE" and a light yellow opaque cap bearing the imprint "30 mg". Imprints are blue.



45 mg hard gelatin capsule consists of a grey opaque body bearing the imprint “ROCHE” and a grey opaque cap bearing the imprint “45 mg”. Imprints are blue.

75 mg hard gelatin capsule consists of a grey opaque body bearing the imprint “ROCHE” and a light yellow opaque cap bearing the imprint “75 mg”. Imprints are blue.

Powder for oral suspension:

The powder is a granulate or clumped granulate with a white to light yellow colour.

Clinical Particulars

Therapeutic Indications

Tamiflu is indicated for the treatment of influenza in adults and children ≥ 1 year of age (see Special Warnings and Special Precautions for Use and Preclinical Safety).

Tamiflu is indicated for the prophylaxis of influenza in adults and children ≥ 1 years of age.

Vaccination is the preferred method of routine prophylaxis against infection with influenza virus.

Dosage and Method of Administration

Tamiflu may be taken with or without food (see Pharmacokinetic Properties). However, Tamiflu taken with food may enhance tolerability in some patients.

Standard dosage

Treatment of influenza

Treatment should begin within the first or second day of onset of symptoms of influenza.

Adults and adolescents

The recommended oral dose of Tamiflu for adults and adolescents ≥ 13 years is 75 mg twice daily, for 5 days. Adults and adolescents ≥ 13 years of age can take Tamiflu capsules. Patients unable to swallow capsules may receive the appropriate dose of Tamiflu oral suspension or home-prepared or pharmacy-compounded Tamiflu capsules (see Patients unable to swallow capsules) to achieve a 75 mg dose.

Infants and Children ≥ 1 to < 13 years of age

The recommended oral dose of Tamiflu for children ≥ 1 year of age is:

Body weight	Recommended dose for 5 days
≤ 15 kg	30 mg twice daily
> 15 to 23 kg	45 mg twice daily
> 23 kg to 40 kg	60 mg twice daily
> 40 kg	75 mg twice daily

Infants and children ≥ 1 year old may receive the required Tamiflu dose in the form of capsules. Patients unable to swallow capsules may receive the appropriate dose of Tamiflu oral suspension or home-prepared or pharmacy-compounded Tamiflu capsules (see Patients unable to swallow capsules).

For the oral suspension a dosing dispenser with 30 mg, 45 mg and 60 mg graduations is provided; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser.

It is recommended that Tamiflu powder for oral suspension be reconstituted by a pharmacist prior to dispensing to the patient (see Special Remarks, Handling and disposal).

Prophylaxis of influenza

Adults and adolescents

The recommended oral dose of Tamiflu for adults and adolescents ≥ 13 years for prophylaxis of influenza following close contact with an infected individual is 75 mg once daily for 10 days. Adults and adolescents ≥ 13 years of age can take capsules. Therapy should begin within two 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 six weeks. The duration of protection lasts for as long as dosing is continued.

Adults and adolescents 13 years of age and older who are unable to swallow capsules may receive the appropriate dose of Tamiflu oral suspension or home-prepared or pharmacy-compounded Tamiflu capsules (see Patients unable to swallow capsules).

Infants and Children ≥ 1 to < 13 years of age

The recommended prophylactic oral dose of Tamiflu for children ≥ 1 year of age is:

Body weight	Recommended dose for 10 days
≤ 15 kg	30 mg once daily
> 15 to 23 kg	45 mg once daily
> 23 kg to 40kg	60 mg once daily
> 40 kg	75 mg once daily

Infants and children ≥ 1 year old may receive the required Tamiflu dose in the form of capsules but those who are unable to swallow capsules may receive the appropriate dose of Tamiflu oral suspension or home-prepared or pharmacy-compounded Tamiflu capsules (see Patients unable to swallow capsules).

For the oral suspension an oral dosing dispenser with 30 mg, 45 mg and 60 mg graduations is provided; the 75 mg dose can be measured using a combination of 30 mg and 45 mg. It is recommended that patients use this dispenser.

It is recommended that Tamiflu powder for oral suspension be reconstituted by a pharmacist prior to dispensing to the patient (see Special Remarks, Handling and disposal).

Patients unable to swallow capsules

When commercially manufactured Tamiflu powder for oral suspension is not readily available, adults, adolescents, children and infants (≥ 1 year of age) who are unable to swallow capsules may receive appropriate doses of Tamiflu either prepared at home by caregivers or prepared by a pharmacist.

Home-prepared, extemporaneous preparation of capsules

Adults and adolescents (13 years and older)

Adults and adolescents who are unable to swallow capsules may receive a 75 mg dose of Tamiflu by following the instructions below.

1. Hold one Tamiflu 75 mg capsule over a small bowl, carefully pull the capsule open and pour the powder into the bowl,
2. Add a suitable, small amount (1 teaspoon maximum) of sweetened food product such as regular or sugar-free chocolate syrup, honey, light brown or table sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce or yogurt to mask the bitter taste of the medication.
3. Stir the mixture well and give the entire contents to the patient. The mixture must be swallowed immediately after its preparation. If there is some mixture left inside the bowl, rinse the bowl with a small amount of water and have the patient drink this remaining mixture. It is not necessary to administer any undissolved white powder as this is inert material.

Children (1 year and older); 15 mg/mL solution

Children who are unable to swallow capsules and require a dose different to that available in capsule form may receive appropriate doses of Tamiflu by following the instructions below.

1. Hold one Tamiflu 75 mg capsule over a small bowl, carefully pull the capsule open and pour the powder into the bowl.
2. Using a graduated syringe, add 5 mL water to the powder. Stir for about two minutes.
3. Draw up into the syringe the correct amount of mixture from the bowl (see table below). The recommended dose is body weight dependent

Push down on the plunger of the syringe, to empty its entire contents into a second bowl. Discard any unused mixture.

Body weight	Recommended dose	Amount of Tamiflu mixture for one dose (15 mg/mL)
≤ 15 kg	30 mg	2 mL
> 15 to 23 kg	45 mg	3 mL
> 23 kg to 40kg	60 mg	4 mL
> 40 kg	75 mg	5 mL

Note: This procedure results in a 15 mg/mL mixture, which is different from Tamiflu Oral Suspension, which has a concentration of 12 mg/mL.

4. In the second bowl, add a suitable, small amount (1 teaspoon maximum) of sweetened food product such as regular or sugar-free chocolate syrup, honey (only for children one year or older), light brown or table sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce or yogurt to the mixture to mask the bitter taste of the medication.
5. Stir this mixture well and give the entire contents of the second bowl to the patient. This mixture must be swallowed immediately after its preparation. If there is some mixture left inside the bowl, rinse the bowl with a small amount of water and have the patient drink this remaining mixture.

Pharmacy-compounded Tamiflu for adults, adolescents, children and infants ≥ 1 year of age

This procedure describes the preparation of a **15 mg/mL** suspension, which will provide one patient with enough medication for a 5-day course of treatment or a 10-day course of prophylaxis.

The pharmacist may compound a suspension (15 mg/mL) from Tamiflu 75 mg capsules using water containing 0.1% w/v sodium benzoate added as a preservative.

First, calculate the total volume needed to be compounded and dispensed to provide a 5-day course of treatment or a 10-day course of prophylaxis for the patient. The total volume of compounded Tamiflu 15 mg/mL suspension required is determined by the weight of the patient according to the recommendation in the table below:

Body Weight (kg)	Total Volume to Compound per Patient Weight (mL)
≤ 15 kg	30 mL
> 15 - 23 kg	40 mL
> 23 - 40 kg	50 mL
> 40 kg	60 mL

Second, determine the number of capsules and the amount of vehicle (water containing 0.1% w/v sodium benzoate added as a preservative) that is needed to prepare the total volume (calculated from the table above: 30 mL, 40 mL, 50 mL or 60 mL) of compounded Tamiflu 15 mg/mL suspension as shown in the table below:

Total Volume of Compounded Suspension to be Prepared	Required Number of Tamiflu 75 mg Capsules (mg of oseltamivir)	Required Volume of Vehicle
30 mL	6 capsules (450 mg)	29 mL
40 mL	8 capsules (600 mg)	38.5 mL
50 mL	10 capsules (750 mg)	48 mL
60 mL	12 capsules (900 mg)	57 mL

Third, follow the procedure below for compounding the suspension (15 mg/mL) from Tamiflu capsules:

- Carefully separate the capsule body and cap and transfer the contents of the required number of Tamiflu capsules into a clean mortar.
- Triturate the granules to a fine powder.
- Add one-third (1/3) of the specified amount of vehicle (water containing 0.1% w/v sodium benzoate added as a preservative) and triturate the powder until a uniform suspension is achieved.
- Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
- 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.
- Repeat the rinsing (Step 5) with the remainder of the vehicle.
- Close the bottle using a child-resistant cap.
- Shake well to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension.

(Note: Undissolved residue may be visible but is comprised of inert ingredients of Tamiflu capsules, which are insoluble. However, the active drug, oseltamivir phosphate, readily dissolves in the specified vehicle and therefore forms a uniform solution.)

9. Put an ancillary label on the bottle indicating “Shake Gently Before Use”.
10. Instruct the parent or caregiver that after the patient has completed the full course of therapy any remaining solution must be discarded. It is recommended that this information be provided by 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 Pharmaceutical Particulars, Stability).

Place a pharmacy label on the bottle that includes the patient’s name, dosing instructions, use by date, medicine name and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions for pharmacy-compounded 15 mg/mL suspension from Tamiflu capsules for infants and children ≥ 1 year old.

Body Weight (kg)	Dose (mg)	Volume per Dose 15 mg/mL	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)
≤ 15 kg	30 mg	2 mL	2 mL twice daily	2 mL once daily
> 15 - 23 kg	45 mg	3 mL	3 mL twice daily	3 mL once daily
> 23 - 40 kg	60 mg	4 mL	4 mL twice daily	4 mL once daily
> 40 kg	75 mg	5 mL	5 mL twice daily	5 mL once daily

Note: This procedure results in a 15 mg/mL suspension, which is different from Tamiflu Oral Suspension, which has a concentration of 12 mg/mL.

Dispense 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 appropriate dose must be mixed by the caregiver with an equal quantity of sweet liquid food, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask the bitter taste.

Special dosage instructions

Patients with renal impairment

Treatment of influenza

No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose is reduced to 75 mg of Tamiflu once daily for 5 days. No dosing recommendation is available for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤ 10 mL/min (see Pharmacokinetics in special populations and Special Warnings and Special Precautions for Use). There is insufficient clinical data available in paediatric patients with renal impairment to make any dosing recommendation.

Prophylaxis of influenza

No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with creatinine clearance between 10 and 30 mL/min receiving Tamiflu, it is recommended that the dose be reduced to 75 mg every other day, or alternatively one 30 mg capsule or 30 mg of suspension

once daily. No dosing recommendation is available for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance ≤ 10 mL/min (see Pharmacokinetics in special populations and Special Warnings and Special Precautions for Use). There is insufficient clinical data available in paediatric patients with renal impairment to make any dosing recommendation.

Patients with hepatic impairment

No dose adjustment is required for patients with hepatic dysfunction in the treatment or prophylaxis of influenza (see Pharmacokinetics in special populations). No studies have been carried out in paediatric patients with hepatic impairment.

Immunocompromised patients

Seasonal prophylaxis in immunocompromised patients ≥ 1 year of age is recommended for 12 weeks. No dose adjustment is necessary.

Elderly

No dose adjustment is required for elderly patients in the treatment or prophylaxis of influenza (see Pharmacokinetics in special populations).

Children

The safety and efficacy of Tamiflu in children under 1 year has not been established (see Pharmacokinetics in special populations). Tamiflu should not be used in children under 1 year of age (see Preclinical Safety).

Contraindications

Hypersensitivity to oseltamivir phosphate or any component of the product.

Special Warnings and Special Precautions for Use

Convulsion and delirium like neuropsychiatric events have been reported during Tamiflu administration in patients with influenza, predominately in children and adolescents. In rare cases, these events resulted in accidental injury. The contribution of Tamiflu to those events is unknown and these have also been reported in patients with influenza who were not taking Tamiflu (see Post Marketing experience).

Patients, especially children and adolescents, should be closely monitored for signs of abnormal behaviour.

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

Dose adjustment is recommended for patients with creatinine clearance of 10 - 30 mL/min for the treatment of influenza and the prophylaxis of influenza. No dosing recommendation is available for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance of ≤ 10 mL/min (see Special dosage instructions and Pharmacokinetics in special populations).

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. For subjects with hereditary fructose intolerance this is above the recommended daily maximum limit of sorbitol.

Interactions with other Medical Products and other Forms of Interaction

Information derived from pharmacology and pharmacokinetic studies of oseltamivir phosphate suggest that clinically significant interactions with other medicines are unlikely.

Oseltamivir phosphate is extensively converted to the active compound by esterases, located predominantly in the liver. Interactions involving competition for esterases have not been extensively reported in the literature. Low protein binding of oseltamivir and the active metabolite do not suggest the probability of displacement interactions.

In vitro studies demonstrated that neither oseltamivir phosphate nor the active metabolite is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases (see Pharmacokinetic properties). There is no mechanistic basis for an interaction with oral contraceptives.

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

Clinically important interactions involving competition for renal tubular secretion are unlikely due to the known safety margin for most of these medicines, 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 approximate 2-fold increase in exposure to the active metabolite due to a decrease in active 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.

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

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 aluminium hydroxides and calcium carbonates).

In phase III treatment and prophylaxis clinical studies, Tamiflu has been administered with commonly used medicines such as ACE inhibitors (enalapril, captopril), thiazide diuretics (bendrofluazide) antibiotics (penicillin, cephalosporin, azithromycin, erythromycin and doxycycline), H₂-receptor blockers (ranitidine, cimetidine), beta-blockers (propranolol), xanthines (theophylline), sympathomimetics (pseudoephedrine), opioids (codeine), corticosteroids, inhaled bronchodilators and analgesic agents (aspirin, 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.

Pregnancy and Lactation

Pregnancy Category B1

In animal reproductive studies in rats and rabbits, no teratogenic effect was observed. Fertility and reproductive toxicity studies have been conducted in rats. There was no evidence of an effect on

fertility at any dose of oseltamivir studied. Foetal exposure in rats and rabbits was approximately 15 - 20% of that of the mother.

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 foetus.

While no controlled clinical trials have been conducted on the use of Tamiflu in pregnant women, limited data available from post-marketing and retrospective observational surveillance do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development.

In lactating rats, oseltamivir and the active metabolite are secreted in milk. Very limited information is available on children breast-fed by mothers taking Tamiflu and on excretion of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and the active metabolite were detected in breast milk at very low levels. Tamiflu should be used in lactating mothers only if the potential benefit for the lactating mother justifies the potential risk of exposure of the medicine to the nursing infant. Tamiflu should therefore be used only if the potential benefit for the lactating mother justifies the potential risk for the nursing infant.

Use in Children

The safety and efficacy of Tamiflu in paediatric patients have not been established in children aged less than 1 year of age. Tamiflu should not be used in children under 1 year of age (see Preclinical safety). No studies have been carried out in paediatric patients with hepatic impairment.

Undesirable Effects

Experience from clinical trials

Adult treatment studies

In a total of 2107 patients (including patients on placebo, 75 mg twice daily Tamiflu and 150 mg twice daily 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 medication 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 $\geq 1\%$ 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	Treatment *		Prophylaxis	
	Placebo <i>n</i> = 1050	Oseltamivir 75 mg twice daily <i>n</i> = 1057	Placebo <i>n</i> = 1434	Oseltamivir 75 mg once daily <i>n</i> = 1480
Nausea (without vomiting)	71 (6.8%)	113 (10.7%)	56 (3.9%)	104 (7.0%)
Vomiting	32 (3.0%)	85 (8.0%)	15 (1.0%)	31 (2.1%)
Diarrhoea	84 (8.0%)	58 (5.5%)	38 (2.6%)	48 (3.2%)
Bronchitis	52 (5.0%)	39 (3.7%)	17 (1.2%)	11 (0.7%)
Abdominal pain	21 (2.0%)	23 (2.2%)	23 (1.6%)	30 (2.0%)
Dizziness	31 (3.0%)	20 (1.9%)	21 (1.5%)	24 (1.6%)
Headache	16 (1.5%)	17 (1.6%)	251 (17.5%)	298 (20.1%)
Insomnia	10 (1.0%)	11 (1.0%)	14 (1.0%)	18 (1.2%)
Cough**	12 (1.1%)	10 (0.9%)	86 (6.0%)	83 (5.6%)
Vertigo**	6 (0.6%)	9 (0.9%)	3 (0.2%)	4 (0.3%)
Fatigue**	7 (0.7%)	8 (0.8%)	107 (7.5%)	117 (7.9%)

* Adverse events included are all events reported the most frequently in the treatment studies in the oseltamivir 75 mg twice daily 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.

In general the adverse event profile in the “at risk” patients in treatment studies was qualitatively similar to healthy young adults.

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, rhinorrhoea, 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.

A 12-week prophylaxis study in 475 immunocompromised patients, including 18 children 1 – 12 years old, showed that the safety profile in the 238 subjects receiving Tamiflu was consistent with that previously observed in Tamiflu prophylaxis clinical trials.

Paediatric treatment studies

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

Adverse events occurring in > 1% of children receiving oseltamivir are listed in Table 2. The most frequently reported adverse event was vomiting. Other events reported more frequently by oseltamivir treated children included abdominal pain, epistaxis, ear disorder and conjunctivitis. These events generally occurred once, resolved despite continued dosing and did not cause discontinuation of treatment in the vast majority of cases.

Table 2: Most frequent adverse events occurring in children aged 1 to 12 years in studies in naturally acquired influenza. Adverse events occurring on treatment in > 1% of paediatric patients enrolled in Phase III trials of Tamiflu treatment of naturally acquired influenza.

Adverse Event	Treatment ^a		Treatment ^b		Prophylaxis ^b	
	Placebo <i>n</i> = 517	Oseltamivir 2 mg/kg twice daily <i>n</i> = 515	Oseltamivir Unit dose ^c <i>n</i> = 158	Oseltamivir Unit dose ^c <i>n</i> = 99	Oseltamivir Unit dose ^c <i>n</i> = 99	Oseltamivir Unit dose ^c <i>n</i> = 99
Vomiting	48 (9.3%)	77 (15.0%)	31 (19.6%)	10 (10.1%)	10 (10.1%)	10 (10.1%)
Diarrhoea	55 (10.6%)	49 (9.5%)	5 (3.2%)	1 (1.0%)	1 (1.0%)	1 (1.0%)
Otitis media	58 (11.2%)	45 (8.7%)	2 (1.3%)	2 (2.0%)	2 (2.0%)	2 (2.0%)
Abdominal pain	20 (3.9%)	24 (4.7%)	3 (1.9%)	3 (3.0%)	3 (3.0%)	3 (3.0%)
Asthma (including aggravated)	19 (3.7%)	18 (3.5%)	-	1 (1.0%)	1 (1.0%)	1 (1.0%)
Nausea	22 (4.3%)	17 (3.3%)	10 (6.3%)	4 (4.0%)	4 (4.0%)	4 (4.0%)
Epistaxis	13 (2.5%)	16 (3.1%)	2 (1.3%)	1 (1.0%)	1 (1.0%)	1 (1.0%)
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%)	3 (1.9%)	-	-	-
Conjunctivitis	2 (0.4%)	5 (1.0%)	-	-	-	-
Dermatitis	10 (1.9%)	5 (1.0%)	1 (0.6%)	-	-	-
Lymphadenopathy	8 (1.5%)	5 (1.0%)	1 (0.6%)	-	-	-
Tympanic membrane disorder	6 (1.2%)	5 (1.0%)	-	-	-	-

^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 Standard dosage).

The adverse events reported in Table 2 are all events reported in the treatment studies with frequency $\geq 1\%$ in the oseltamivir 75 mg twice daily group.

Paediatric Prophylaxis

Paediatric 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. In a separate 6-week paediatric prophylaxis study (*n* = 49) the adverse events noted were consistent with those previously observed (see Table 2).

Post-marketing experience

Skin and subcutaneous tissue disorders: rare cases of hypersensitivity reactions such as allergic skin reactions including dermatitis, rash, eczema, urticaria, and very rare cases of erythema multiforme, Stevens-Johnson-Syndrome and toxic epidermal necrolysis are reported. Also, allergy, anaphylactic /anaphylactoid reactions and face oedema are reported rarely.

Hepatobiliary disorders: very rare reports of hepatitis and elevated liver enzymes have been reported in patients with influenza like illness receiving oseltamivir.

Psychiatric disorders/nervous system disorders: convulsion and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares) have been reported during Tamiflu administration in patients with influenza, predominately in children and adolescents. These events often had an abrupt onset and rapid resolution. In rare cases, these events resulted in accidental injury, and some resulted in a fatal outcome, however, the contribution of Tamiflu to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Tamiflu.

Patients with influenza should be closely monitored for signs of abnormal behaviour throughout the treatment period.

Gastro-intestinal disorders: In rare cases gastro-intestinal bleedings were observed after the use of Tamiflu. In particular, haemorrhagic colitis was reported that subsided when the course of influenza abated or treatment with Tamiflu was interrupted.

Overdose

At present there has been no experience with overdose, however the anticipated manifestations of acute overdose would be nausea, with or without accompanying emesis. Single doses of up to 1000 mg of Tamiflu have been well tolerated apart from nausea and/or vomiting.

Pharmacological Properties and Effects

Pharmacodynamic Properties

Mechanism of action

Oseltamivir phosphate is a pro-drug of oseltamivir carboxylate, a potent and selective inhibitor of influenza virus neuraminidase enzymes. 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.

Oseltamivir carboxylate inhibits the neuraminidases of influenza viruses of both types A and B. Concentrations of oseltamivir carboxylate required to inhibit the enzyme activity by 50% (IC₅₀) are in the low nanomolar range. Oseltamivir carboxylate also inhibits influenza virus infection and replication *in-vitro* and inhibits influenza virus replication and pathogenicity *in-vivo*.

Oseltamivir carboxylate reduces shedding of both influenza A and B virus by inhibiting the release of infectious virus from infected cells.

Clinical / Efficacy studies

Clinical efficacy of Tamiflu has been demonstrated in human experimental infection studies and phase III studies in naturally occurring influenza.

In studies in naturally acquired and experimental influenza, treatment with Tamiflu did not impair normal humoral antibody response to infection. Antibody response to inactivated vaccine is not expected to be affected by treatment with Tamiflu.

Trials in naturally occurring influenza

In phase III clinical trials conducted in the 1997 - 1998 Northern Hemisphere influenza season, patients were treated with Tamiflu for up to 40 hours after reported onset of symptoms. In these studies, 97% of patients were infected with influenza A and 3% with influenza B. Tamiflu treatment significantly reduced the duration of clinically relevant signs and symptoms of influenza by 32 hours. Disease severity in patients with confirmed influenza taking Tamiflu was also reduced by 38% compared to placebo. Moreover, Tamiflu reduced the incidence of complications associated with influenza treated with antibiotic therapy in otherwise healthy young adults by approximately 50%. These complications include bronchitis, pneumonia, sinusitis and otitis media. In these phase III clinical trials there was clear evidence of efficacy in the secondary endpoints related to antiviral activity in terms of both reduction of duration of virus shedding and reduction in the AUC of viral titres.

Data from a treatment study in the elderly population have shown that Tamiflu 75 mg twice daily for five days was associated with a reduction in median duration of illness that was clinically relevant, and similar to that seen in the younger adult treatment studies. In a separate study, patients aged > 13 years with influenza and co-existing chronic cardiac and/or respiratory disease received the same regimen of either Tamiflu or placebo. No difference in the median time to alleviation of all symptoms was seen between patients taking Tamiflu or placebo, however the duration of febrile illness was reduced by approximately one day by receipt of Tamiflu. The proportion of patients shedding virus on days 2 and 4 was also markedly reduced by active treatment. There was no difference in the safety profile of Tamiflu in the at-risk populations compared to the general adult population.

Treatment of influenza in children

One double-blind placebo controlled treatment trial was conducted in otherwise healthy children (65% influenza positive) aged 1 to 12 years (mean age 5.3), who had fever ($\geq 100^{\circ}$ F) plus one respiratory symptom (cough or coryza) when influenza virus was known to be circulating in the community. In this study 67% of influenza-infected patients were infected with influenza A and 33% with influenza B. Tamiflu treatment, started within 48 hours of onset of symptoms, significantly reduced the duration of illness by 35.8 hours compared to placebo. Duration of illness was defined as time to alleviation of cough, nasal congestion, resolution of fever, and return to normal health and activity. The proportion of patients developing acute otitis media was reduced by 40% in children receiving Tamiflu (29/183) vs placebo (53/200). Children receiving Tamiflu returned to normal health and activity almost 2 days earlier than those receiving placebo.

A second study was completed in 334 asthmatic children aged 6 to 12 years old of which 53.6% were influenza-positive. In the oseltamivir-treated group the median duration of illness was not reduced significantly. By day 6 (the last day of treatment) FEV₁ had increased by 10.8% in the oseltamivir-treated group compared to 4.7% on placebo ($p = 0.0148$) in this population.

Trials for prophylaxis of influenza

Prophylaxis of influenza in adults and adolescents

The efficacy of Tamiflu in preventing naturally occurring influenza illness has been demonstrated in three seasonal prophylaxis studies and two post exposure prophylaxis study in households. The primary efficacy parameter for all these studies was the incidence of laboratory confirmed clinical influenza. Laboratory confirmed clinical influenza was defined as oral temperature $\geq 99.0^{\circ}$ F/ 37.2° C plus at least one respiratory symptom (cough, sore throat, nasal congestion) and at least one constitutional symptom (aches and pain, fatigue, headache, chills/sweats), all recorded within 24 hours, plus either a positive virus isolation or a fourfold increase in virus antibody titers from baseline.

In a pooled analysis of two seasonal prophylaxis studies in healthy unvaccinated adults (aged 18 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 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 post-exposure prophylaxis study, household contacts (aged ≥ 13 years) who had no laboratory evidence of influenza at baseline, and who were living with an index case subsequently shown to have had influenza infection, were randomized to treatment (the ITTIINAB population). In this population Tamiflu 75 mg administered once daily within 2 days of onset of symptoms in the index case and continued for 7 days, reduced the incidence of laboratory confirmed clinical influenza in the contacts from 12% (24/200) in the placebo group to 1% (2/205) for the Tamiflu group (risk reduction 91.9%, $p < 0.001$). For the study population as a whole (the ITT population), including contacts of index cases in whom influenza infection was not confirmed, the incidence of laboratory confirmed clinical influenza was reduced from 7.4% (34/462) in the placebo group to 0.8% (4/493) for the Tamiflu group (risk reduction 89%, $p < 0.001$). Index cases did not receive Tamiflu in the study. In the ITT population 13.9% of contacts in the placebo group and 11.4% of contacts in the Tamiflu group had been vaccinated.

The efficacy of Tamiflu in preventing naturally occurring influenza illness in adults and children has also been demonstrated in a post exposure prophylaxis study conducted in households in which index cases with rapid onset of fever, cough and/or coryza received twice daily treatment with Tamiflu for 5 days. The primary efficacy parameter for this study was the percentage of households with at least one secondary case of febrile laboratory confirmed influenza illness. A laboratory confirmed case was defined as a febrile illness (oral/otic temperature ≥ 100.0 °F/37.8 °C) plus cough and/or coryza, confirmed to be influenza by either detection of viral shedding within 2 days before or after the time that the fever was reported, and/or a four fold increase in influenza virus antibody titers from baseline to the day 30 sample. Household contacts were randomized (by household) to receive either once daily prophylaxis with oseltamivir for 10 days (Group P) or to receive treatment for 5 days upon the emergence of influenza-like illness (Group T).

In households with an infected index case and where there was no laboratory evidence of influenza among the contacts at baseline (ITTIINAB), there was a 78.8% ($p = 0.0008$) reduction in households with infected contacts in Group T 22% (20/89) versus Group P 5% (4/84). In the population as a whole (ITT), including contacts of index cases in whom influenza infection was not confirmed, the prophylactic efficacy protection was 62.7% ($p = 0.0042$), Group T 20% (27/137) versus Group P 7% (10/137). A significant number of children aged 1 - 12 participated in this study, both as index cases and as contacts. In the ITTIINAB population of paediatric contacts, there was an 80.1% ($p = 0.0206$) reduction in the incidence of laboratory confirmed influenza in Group T 21% (15/70) versus Group P 4% (2/47). A similar reduction in clinical influenza was seen in the subset of paediatric contacts that also had paediatric index cases.

Prophylaxis of influenza in children

The efficacy of Tamiflu in preventing naturally occurring influenza illness has been demonstrated in a postexposure prophylaxis study in households that included children aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza. In this study, Tamiflu oral suspension 30 mg to 75 mg once daily taken for 10 days among children who were not already shedding virus at baseline reduced the

incidence of laboratory-confirmed clinical influenza from 21% (15/70) in the group not receiving prophylaxis to 4% (2/47) in the group receiving prophylaxis.

Prophylaxis of influenza in immunocompromised patients

A double-blind, placebo controlled study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised subjects, including 18 children 1 – 12 years old. Laboratory-confirmed clinical influenza, as defined by RT-PCR plus oral temperature ≥ 37.2 °C/99.0 °F plus cough and/or coryza, all recorded within 24 hours, was evaluated. Among subjects who were not already shedding virus at baseline, Tamiflu reduced the incidence of laboratory-confirmed clinical influenza from 3.0% (7/231) in the group not receiving prophylaxis to 0.4% (1/232) in the group receiving prophylaxis (see Table 3).

Table 3: Incidence of influenza infection in immunocompromised patients

Population	Placebo n/N (%)	Tamiflu 75 mg once daily n/N (%)	Treatment effect ^a	95% CI for difference in proportions between treatments ^b	p-value ^c
Overall ITT	7/238 (2.9%)	5/237 (2.1%)	28.3%	-2.3% to 4.1%	0.772
ITTII	7/238 (2.9%)	2/237 (0.8%)	71.3%	-0.6% to 5.2%	–
ITTIINAB	7/231 (3.0%)	1/232 (0.4%)	85.8%	0.1% to 5.7%	–

^a Treatment effect = (1 – Relative Risk)*100%

^b Calculated using Newcombe’s method of combining Wilson score intervals without continuity correction

^c Comparison of Placebo versus Tamiflu using Fisher’s exact test

ITTII = intent-to-treat index-infected

ITTIINAB = intent-to-treat index-infected, not infected at baseline.

Viral resistance

There has been no evidence for emergence of resistance associated with the use of Tamiflu in clinical studies conducted to date in post exposure (7 days), post exposure within household groups (10 days) and seasonal (42 days) prophylaxis of influenza in immunocompetent persons. There was no resistance observed during a 12-week seasonal prophylaxis study in immunocompromised subjects.

The risk of emergence of resistance in clinical use in the treatment of influenza has been extensively examined. In all clinical studies in naturally acquired infection, 0.32% (4/1245) of adults and adolescents and 4.1% (19/464) of children aged 1 to 12 years were found to transiently carry influenza virus with decreased neuraminidase susceptibility to oseltamivir carboxylate. Patients carrying resistant virus cleared it normally and showed no clinical deterioration. All resistant genotypes are disadvantaged compared to the corresponding wild-type isolate and are likely to be less contagious in man. There is no evidence for resistance in influenza B *in vitro* or in clinical trials.

Pharmacokinetic Properties

Absorption

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to the active metabolite. Plasma concentrations of the active metabolite are measurable within 30 minutes, reach near maximal levels in 2 to 3 hours post dose, and substantially exceed (> 20-fold) those of the pro-drug. At least 75% of an oral dose reaches the systemic circulation as the active metabolite. Plasma concentrations of active metabolite are proportional to dose and are unaffected by co-administration with food (see Dosage and Method of Administration).

Distribution

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

The active moiety reaches all key sites of influenza infection as shown by studies in the ferret, rat and rabbit. In these studies, anti-viral concentrations of the active metabolite were seen in the lung, bronchoalveolar lavage, nasal mucosa, middle ear and trachea following oral administration of doses of oseltamivir phosphate.

The binding of the active metabolite to human plasma protein is negligible (approximately 3%). The binding of the pro-drug to human plasma protein is 42%. These levels are insufficient to cause significant interactions.

Metabolism

Oseltamivir phosphate 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 (see Interactions with other Medical Products and other Forms of Interaction).

Elimination

Absorbed oseltamivir is primarily (> 90%) eliminated by conversion to the active metabolite. The active metabolite is not further metabolised 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 substance 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 faeces.

Pharmacokinetics in special populations

Patients with 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.

Treatment of influenza

No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with a creatinine clearance of 10 to 30 mL/min, it is recommended that the dose be reduced to 75 mg of Tamiflu once daily for 5 days. No dosing recommendation is available for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients

with creatinine clearance \leq 10mL/min (see Special dosage instructions and Special Warnings and Special Precautions for Use).

Prophylaxis of influenza

In patients with creatinine clearance between 10 to 30 mL/min receiving Tamiflu it is recommended that the dose be reduced to 75 mg of Tamiflu every other day or 30 mg suspension every day. No dosing recommendation is available for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance \leq 10 mL/min (see Special dosage instructions and Special Warnings and Special Precautions for Use).

Patients with hepatic impairment

In-vitro studies have shown that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite significantly decreased in patients with hepatic impairment (see Special dosage instructions).

Elderly

Exposure to the active metabolite at steady state was 25 to 35% higher in elderly (age range 65 to 78) compared to young adults who were given comparable doses of Tamiflu. Half-lives observed in the elderly were similar to those seen in young adults. On the basis of exposure and tolerability, dosage adjustments are not required for elderly patients for either the treatment or prophylaxis of influenza (see Special dosage instructions).

Children \geq 1 year of age

The pharmacokinetics of Tamiflu have been evaluated in a single dose pharmacokinetic studies in children aged 1 to 16 years. Multiple dose pharmacokinetics were studied in a small number of children aged 3 to 12 enrolled in a clinical trial. The rate of clearance of the active metabolite, corrected for bodyweight, was faster in younger children, than in adults, resulting in lower exposure in these children for a given mg/kg dose. Doses of 2 mg/kg and unit doses of 30 and 45 mg, administered to children in the appropriate categories according to the recommendation in the Dosage and Method of Administration section yield 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 children over 12 years of age are similar to those in adults.

Preclinical safety

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Three studies for carcinogenic potential (2 year rat and mouse studies with oseltamivir, and a 6 month transgenic Tg:AC mouse assay performed with the active metabolite) were negative.

Teratology studies have been conducted in rats and rabbits at doses up to 1500 mg/kg/day and 500 mg/kg/day, respectively. No effects on embryo-foetal development were observed. A rat fertility study up to a dose of 1500 mg/kg/day demonstrated no adverse effects on either sex. In pre-/post-natal rat studies, prolonged parturition was noted at 1500 mg/kg/day: the safety margin between human exposure and the highest no effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20% of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in milk. Limited data indicate that oseltamivir and the active metabolite are excreted in human milk. Extrapolation of the animal data provides estimates of 0.01 mg/day and 0.3 mg/day for the respective compounds.

A potential for skin sensitisation to oseltamivir was observed in a “maximisation” test in guinea pigs. Approximately 50% of the animals treated with the unformulated active ingredient showed erythema after challenging the induced animals. Reversible irritancy of the rabbits’ eyes was detected.

Very high oral single doses of oseltamivir phosphate had no effect in adult rats, however, such doses resulted in toxicity in juvenile seven-day-old rat pups, including death. These effects were seen at doses of 657 mg/kg/day and higher. No adverse effects were seen following a single dose of 500 mg/kg, nor with chronic dosing of 500 mg/kg/day from day 7 to day 21 *post partum*.

Pharmaceutical Particulars

Stability

Capsules:

30 mg, 45 mg and 75 mg: Do not store above 25 °C

Powder for oral suspension:

After reconstitution, the suspension can be stored at room temperature (below 25 °C) for up to 10 days or in a refrigerator (2 – 8 °C) for up to 17 days. Tamiflu oral suspension should not be frozen.

These medicines should not be used after the expiry date shown on the pack.

Home-prepared mixture (by opening 75 mg capsules):

Home-prepared Tamiflu mixture must be swallowed immediately after preparation.

Pharmacy-compounded suspension:

After pharmacy compounding of Tamiflu capsules the 15 mg/mL suspension can be stored at room temperature (below 25 °C) for up to 3 weeks (21 days) or in a refrigerator (2 - 8 °C) for up 6 weeks. Pharmacy-compounded Tamiflu suspension should not be frozen.

Special Remarks

Handling and disposal

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Preparation of Tamiflu 12 mg/mL powder for oral suspension

It is recommended that Tamiflu powder for oral suspension be reconstituted by the pharmacist prior to dispensing to the patient (see Dosage and Method of Administration):

1. Tap the closed bottle several times to loosen the powder.
2. Measure 52 mL of water. Use the measuring cup (where provided) and fill it to the indicated level.



3. Add all 52 mL of water for reconstitution to the bottle and shake the closed bottle well for 15 seconds. The final reconstituted volume is 75 mL.
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.

The oral dispenser should be dispensed to the patient. It is recommended that the date of expiration of the reconstituted suspension be written on the bottle label.

Medicine Classification

Prescription medicine.

Tamiflu (oseltamivir) is subject to classification conditions. For up to date classification of Tamiflu please refer to www.medsafe.govt.nz/profs/class/classintro.asp.

Packs

Tamiflu capsules 30 mg, 45 mg and 75 mg

blister pack of 10 capsules

Tamiflu powder for oral suspension 12 mg/mL

bottle pack with 30 g of powder, a measuring cup, a bottle adaptor and a dosing syringe

Note: Tamiflu 30 mg and 45 mg capsules are currently not available.

Name and Address

Roche Products (New Zealand) Limited
PO Box 12492
Penrose
AUCKLAND

Telephone: (09) 635 1500
Telefax: (09) 635 1522
Toll Free: 0800 656 464

Date of Preparation

8 April 2011