# PROFESSIONAL INFORMATION

## SCHEDULING STATUS

S4

## PROPRIETARY NAME AND DOSAGE FORM

**Tamiflu® 30 mg** Capsules

**Tamiflu® 45 mg** Capsules

**Tamiflu® 75 mg** Capsules

**Tamiflu® 6 mg/mℓ** Powder for Oral Suspension

## COMPOSITION

**Tamiflu 30 mg** Capsules: Each capsule contains oseltamivir phosphate equivalent to 30 mg oseltamivir base.

Other ingredients are: pregelatinised starch, povidone, sodium croscarmellose, sodium stearyl fumarate and talc. The capsule shell contains gelatin, yellow iron oxide (E172), red iron oxide (E172) and titanium dioxide (E171). The printing ink contains shellac (904), titanium dioxide (E171) and FD and C Blue 2 (Indigo carmine, E132).

**Tamiflu 45 mg** Capsules: Each capsule contains oseltamivir phosphate equivalent to 45 mg oseltamivir base.

Other ingredients are: pregelatinised starch, povidone, sodium croscarmellose, sodium stearyl fumarate and talc. The capsule shell contains gelatin, black iron oxide (E172) and titanium dioxide (E171). The printing ink contains shellac (904), titanium dioxide (E171) and FD and C Blue 2 (Indigo carmine, E132).

**Tamiflu 75 mg** Capsules: Each capsule contains oseltamivir phosphate equivalent to 75 mg oseltamivir base.

Other ingredients are: pregelatinised starch, povidone, sodium croscarmellose, sodium stearyl fumarate and talc. The capsule shell contains gelatin, black iron oxide (E172), yellow iron oxide

(E172), red iron oxide (E172) and titanium dioxide (E171). The printing ink contains shellac (904), titanium dioxide (E171) and FD and C Blue 2 (Indigocarmine, E132).

**Tamiflu 6 mg/mℓ** Powder for Oral Suspension: Each 1 g of powder for oral suspension contains oseltamivir phosphate equivalent to 30 mg oseltamivir base.

Each 1 mℓ of the reconstituted suspension contains 6 mg oseltamivir and sodium benzoate 0,05 % m/v as preservative.

Other ingredients are: saccharin sodium, sodium dihydrogen citrate, sorbitol, titanium dioxide (E171), tutti frutti flavour and xanthan gum.

Tamiflu Powder for Oral Suspension contains sorbitol.

## CATEGORY AND CLASS

A 20.2.8 Antiviral agents

## PHARMACOLOGICAL ACTION

### Pharmacodynamic properties

Oseltamivir phosphate is a pro-drug and selective inhibitor of influenza virus neuraminidase enzymes. Viral neuraminidase is essential for the release of recently formed virus particles from infected cells, and the further spread of infectious virus.

The active metabolite of oseltamivir inhibits neuraminidases of influenza viruses of both types A and B.

The active metabolite also inhibits influenza virus growth *in vitro* and inhibits influenza virus replication and pathogenicity *in vivo*. The active metabolite reduces shedding of both influenza A and B virus by inhibiting the release of infectious virus from infected cells.

### 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 DIRECTIONS FOR USE).

***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, antiviral 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 medicine 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).

***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 - 10 hours in most subjects. The active medicine 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 radio-labelled dose is eliminated in faeces.

**Pharmacokinetics in Special Populations**

***Patients with renal impairment***

Administration of 100 mg of oseltamivir 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 60 mℓ/min. In patients with a creatinine clearance of > 30 - 60 mℓ/min, it is recommended that the dose be reduced to 30 mg of oseltamivir twice daily for 5 days. In patients with a creatinine clearance of 10 - 30 mℓ/min, it is recommended that the dose be reduced to 30 mg of oseltamivir once daily for 5 days.

In patients undergoing routine haemodialysis an initial dose of 30 mg of oseltamivir can be administered prior to the start of dialysis in patients with influenza symptoms during the 48 hours between dialysis sessions. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every haemodialysis session. For peritoneal dialysis an initial dose of 30 mg of oseltamivir administered prior to the start of dialysis followed by further 30 mg doses administered every 5 days is recommended for treatment (see DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS). The pharmacokinetics of oseltamivir have not been studied in patients with “end-stage renal disease” (i.e., creatinine clearance of < 10 mℓ/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group.

*Prophylaxis of influenza*

No dose adjustment is necessary for patients with creatinine clearance above 60 mℓ/min. In patients with a creatinine clearance of > 30 - 60 mℓ/min, it is recommended that the dose be reduced to 30 mg of oseltamivir once daily. In patients with creatinine clearance between 10 and 30 mℓ/min receiving oseltamivir it is recommended that the dose be reduced to 30 mg of oseltamivir every other day. In patients undergoing routine haemodialysis an initial dose of 30 mg of oseltamivir can be administered prior to the start of dialysis. To maintain plasma

concentrations at a therapeutic level, a dose of 30 mg should be administered after every alternate haemodialysis session. For peritoneal dialysis an initial dose of 30 mg of oseltamivir administered prior to the start of dialysis followed by further 30 mg doses administered every 7 days is recommended for prophylaxis (see DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS). The pharmacokinetics of oseltamivir have not been studied in patients with "end-stage renal disease" (i.e., creatinine clearance of < 10 mℓ/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group.

***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 expected to be significantly decreased in patients with mild or moderate hepatic impairment (see DOSAGE AND DIRECTIONS FOR USE). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

***Elderly***

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

***Children ≥ 1 year of age***

The pharmacokinetics of oseltamivir have been evaluated in single dose pharmacokinetic studies in children aged 1 to 16 years. Multiple dose pharmacokinetics was studied in a small number of children aged 3 - 12 years enrolled in a clinical trial. The rate of clearance of the active metabolite, corrected for bodyweight, was faster in children than in adults, resulting in lower exposure in these children for a given mg/kg dose. The rate of clearance of the active

metabolite increased with decreasing age over the age range 3 to 16 years. Doses of 2 mg/kg 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.

***Infants 6 to 12 months of age***

Limited pharmacokinetic and safety data are available for infants less than 2 years of age. Pharmacokinetic modelling was undertaken using these data in addition to data from studies in adults and children older than 1 year of age. The results demonstrate that doses of 3 mg/kg twice daily for infants aged 6 to 12 months provide exposures similar to those shown to be clinically efficacious in adults and children > 1 year of age (see INDICATIONS and DOSAGE AND DIRECTIONS FOR USE).

## INDICATIONS

*TREATMENT*

Tamiflu is indicated for the treatment of influenza in adults and children ≥ 1 year of age (see WARNINGS AND SPECIAL PRECAUTIONS and *Special Dosage Instructions)*.

PANDEMIC USE: Tamiflu is indicated for the treatment of infants 6 - 12 months of age during a pandemic influenza outbreak only, and not for endemic (seasonal) influenza use (see WARNINGS AND SPECIAL PRECAUTIONS and *Pharmacokinetics in Special Populations)*.

*PROPHYLAXIS*

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

## CONTRAINDICATIONS

Hypersensitivity to oseltamivir phosphate or to any component of Tamiflu.

## WARNINGS AND SPECIAL PRECAUTIONS

Neuropsychiatric events such as convulsions, abnormal and inappropriate behaviour, disturbances in consciousness, hallucinations and delirium have been reported during Tamiflu

administration in patients with influenza. In some cases, the delirium resulted in accidental self-injury and death. These events occurred mostly within the first few days of taking Tamiflu.

Patients, and especially paediatric and adolescent patients, taking Tamiflu should be carefully 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. Tamiflu is not a substitute for influenza vaccination.

Resistance of influenza viruses to Tamiflu have been reported. The prevalence of virus resistance and virus strains on subtypes differs between countries and seasons. In South Africa where H1N1 viruses predominated among circulating strains, 100 % [225/225] of H1N1 viruses tested in 2008 were resistant to Tamiflu. The resistance of the predominant virus to Tamiflu generally changes from season to season. Updated local surveillance data from the National Institute for Communicable Diseases (NICD) should be consulted for information on seasonal prevalence of medicine resistant viruses.

Based on limited pharmacokinetic and safety data, Tamiflu may only be used in infants 6 - 12 months of age for treatment during a pandemic influenza outbreak. The treating medical practitioner should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure that there is a potential benefit to the child.

**Renal impairment**

Dose adjustment is recommended for patients with creatinine clearance of 10 - 60 mℓ/min for the treatment of influenza and the prophylaxis of influenza. No dosing recommendation is available for patients with end-stage renal disease and for patients with creatinine clearance of ≤ 10 mℓ/min (see DOSAGE AND DIRECTIONS FOR USE).

Tamiflu should not be used in children under 1 year of age, other than during a pandemic influenza outbreak.

**Effects on the ability to drive and use machines**

It is not known whether Tamiflu could affect the ability to drive a car or operate machinery. However, if symptoms such as delirium or fever are experienced while taking Tamiflu, patients should be advised not drive or use machines until the symptoms disappear.

**Sugars**

Tamiflu Powder for Oral Suspension contains sorbitol which may have a laxative effect.

**INTERACTIONS**

Information derived from pharmacology and pharmacokinetic studies of Tamiflu suggest that clinically significant medicine interactions are unlikely.

Tamiflu 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 Tamiflu and the active metabolite do not suggest the probability of medicine displacement interactions.

*In vitro* studies demonstrated that neither Tamiflu 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 medicines has no effect on plasma levels of Tamiflu 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 Tamiflu, its active metabolite, or paracetamol.

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

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), $H_2$-receptor blockers (ranitidine, cimetidine), beta-blockers (propranolol), xanthines (theophylline), sympathomimetics (pseudoephedrine), opioids (codeine), corticosteroids, inhaled bronchodilators, and analgesic medicines (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.

**HUMAN REPRODUCTION**

Safety in pregnancy and lactation has not been established.

In animal reproductive studies in rats and rabbits, no teratogenic effect was observed.

*Pregnancy*

No controlled clinical trials have been conducted on the use of Tamiflu in pregnant women.

*Lactation*

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. Limited information is available on infants breastfed by mothers taking Tamiflu and on excretion of Tamiflu in breast milk. Limited data demonstrated that low levels of oseltamivir and the active metabolite were detected in breast milk. Safety in humans has not been demonstrated in

children of breastfeeding women using Tamiflu. Mothers on treatment with Tamiflu should not breastfeed their infants.

## DOSAGE AND DIRECTIONS FOR USE

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 Capsules in adults and adolescents ≥ 13 years is a 75 mg capsule twice daily, for 5 days.

Adults and adolescents ≥ 13 years of age who are unable to swallow capsules may receive a dose of 75 mg Tamiflu Powder for Oral Suspension twice daily for 5 days.

*Children:* Children weighing > 40 kg who are able to swallow capsules, may also receive treatment with a 75 mg capsule twice daily or one 30 mg capsule plus one 45 mg capsule twice a day as an alternative to the recommended dose of Tamiflu Powder for Oral Suspension (see below).

*The recommended oral dose of Tamiflu Powder for Oral Suspension for children ≥ 1 year of age is:*

| ***Body weight*** | ***Recommended dose for 5 days* - Capsules** | ***Amount of 6 mg/mℓ Oral Suspension*** |
|---|---|---|
| ≤ 15 kg | 30 mg twice daily | 5,0 mℓ twice daily |
| > 15 to 23 kg | 45 mg twice daily | 7,5 mℓ twice daily |
| > 23 kg to 40 kg | 60 mg twice daily | 10,0 mℓ twice daily |
| > 40 kg | 75 mg twice daily | 12,5 mℓ twice daily |

A 10 mℓ oral dosing syringe is provided for the 6 mg/mℓ oral suspension for children ≥ 1 year of age.

The 75 mg dose can be measured using a combination of 30 mg and 45 mg.

It is recommended that Tamiflu Powder for Oral Suspension be constituted by a pharmacist prior to dispensing to the patient.

*The recommended oral dose of Tamiflu for children 6 - 12 months of age:*

Based on limited pharmacokinetic data currently available, a dosage of 3 mg/kg twice daily in children 6 - 12 months of age provides plasma exposure to the active metabolite in the majority of patients similar to that shown to be clinically efficacious in older children and adults.

Recommended volumes of reconstituted oral suspension to be drawn up into an oral syringe (3 mg/kg body weight) are shown in the table below:

| ***Body Weight (kg)*** | ***Tamiflu (mg)*** | ***Rounded volume of 6 mg/mℓ suspension*** |
|---|---|---|
| 6 | 18 | 3 mℓ |
| 7 | 21 | 3,5 mℓ |
| 8 | 24 | 4 mℓ |
| 9 | 27 | 4,5 mℓ |
| ≥ 10 | 30 | 5 mℓ |

Use the smallest graduated oral syringe that will accurately deliver the appropriate volume.

The recommended treatment dose for infants 6 - 12 months is 3 mg/kg twice daily for 5 days, during a pandemic influenza outbreak only, and not for endemic (seasonal) influenza use (see *Pharmacokinetics in Special Populations)*.

***Prophylaxis of influenza***

*Adults and adolescents*

The recommended oral dose of Tamiflu for prophylaxis of influenza following close contact with an infected individual is 75 mg once daily for at least 10 days. 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.

*Children ≥ 1 year of age*

Children weighing > 40 kg, who are able to swallow capsules, may also receive prophylaxis with a 75 mg capsule once daily or one 30 mg capsule plus one 45 mg capsule once a day, for 10 days as an alternative to the recommended dose of Tamiflu 6 mg/mℓ Powder for Oral Suspension.

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

| ***Body Weight*** | ***Recommended dose for 10 days*** | ***Amount of 6 mg/mℓ Oral Suspension*** |
|---|---|---|
| ≤ 15 kg | 30 mg once daily | 5,0 mℓ once daily |
| > 15 to 23 kg | 45 mg once daily | 7,5 mℓ once daily |
| > 23 kg to 40 kg | 60 mg once daily | 10,0 mℓ once daily |
| > 40 kg | 75 mg once daily | 12,5 mℓ once daily |

A 10 mℓ oral dosing syringe is provided for the 6 mg/mℓ oral suspension.

The 75 mg dose can be measured using a combination of 30 mg and 45 mg.

It is recommended that Tamiflu powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient (see *Special Instructions for Use, Handling and Disposal*).

**Special Dosage Instructions**

***Patients with renal impairment***

*Treatment of influenza:* No dose adjustment is necessary for patients with creatinine clearance above 60 mℓ/min. In patients with a creatinine clearance of > 30 - 60 mℓ/min, it is recommended that the treatment dose be reduced to 30 mg of Tamiflu twice daily for 5 days. In patients with a creatinine clearance of 10 - 30 mℓ/min, it is recommended that the dose be reduced to 30 mg of

Tamiflu once daily for 5 days. In patients undergoing routine haemodialysis an initial dose of 30 mg Tamiflu can be administered prior to the start of dialysis if influenza symptoms develop during the 48 hours between dialysis sessions. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every haemodialysis session. For peritoneal dialysis an initial dose of 30 mg of Tamiflu administered prior to the start of dialysis followed by further 30 mg doses administered every 5 days is recommended for treatment (see *Pharmacokinetics in Special Populations* and WARNINGS AND SPECIAL PRECAUTIONS). The pharmacokinetics of Tamiflu have not been studied in patients with "end-stage renal disease" (i.e. creatinine clearance < 10 mℓ/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group.

*Prophylaxis of influenza:* No dose adjustment is necessary for patients with creatinine clearance above 60 mℓ/min. In patients with a creatinine clearance of > 30 - 60 mℓ/min, it is recommended that the dose be reduced to 30 mg of Tamiflu once daily. In patients with a creatinine clearance between 10 and 30 mℓ/min receiving Tamiflu, it is recommended that the dose be reduced to 30 mg of Tamiflu every other day. In patients undergoing routine haemodialysis an initial dose of 30 mg of Tamiflu can be administered prior to the start of dialysis. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every alternate haemodialysis session. For peritoneal dialysis an initial dose of 30 mg of Tamiflu administered prior to the start of dialysis followed by further 30 mg doses administered every 7 days is recommended for prophylaxis (see *Pharmacokinetics in Special Populations* and WARNINGS AND SPECIAL PRECAUTIONS). The pharmacokinetics of Tamiflu have not been studied in patients with "end-stage renal disease" (i.e., creatinine clearance < 10 mℓ/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group.

***Patients with hepatic impairment***

No dose adjustment is required for patients with mild or moderate hepatic dysfunction in the treatment or prophylaxis of influenza (see *Pharmacokinetics in Special Populations*). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

***Immuno-compromised patients***

Seasonal prophylaxis in immuno-compromised patients 1 year of age and older 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, other than during a pandemic influenza outbreak.

**Instructions for use and handling**

It is recommended that Tamiflu Powder for Oral Suspension should be reconstituted by the pharmacist prior to its dispensing to the patient.

**Preparation of 6 mg/mℓ Oral Suspension**

To obtain 64,7 mℓ (60 mℓ retrievable) of suspension:

1. Tap the closed bottle gently several times to loosen the powder.
2. Measure 55 mℓ of water. Use the measuring cup (where provided) and fill it to the indicated level.
3. Add all 55 mℓ of water for constitution to the bottle and shake the closed bottle well for 15 seconds.
4. Remove the child-resistant cap and push bottle adapter into neck of bottle.
5. Close bottle with the child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap.

**When Tamiflu Powder for Oral Suspension is not available**

During situations when commercially manufactured Tamiflu powder for oral suspension is not readily available, adults, adolescents or children who are unable to swallow capsules may receive appropriate doses of Tamiflu by opening capsules and pouring the contents of capsules into a suitable, small amount (1 teaspoon (5 mℓ) maximum) of sweetened food product such as regular or sugar-free chocolate syrup, honey (only for children two years or older), light brown or table sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce or yoghurt to mask the bitter taste. The mixture should be stirred and the entire contents given to the patient. The mixture must be swallowed immediately after its preparation.

*When using the 30 mg and 45 mg capsules*: follow these instructions to ensure proper dosing:

1. Determine the number of capsules that are needed to prepare a mixture with this procedure:

| ***Body Weight**** | ***Recommended number of capsule(s) needed to obtain the recommended doses for 5 days treatment*** | ***Required number of capsule(s) needed to obtain the recommended doses for prevention (10 days)*** |
|---|---|---|
| Less than or equal to 15 kg | 1 capsule of 30 mg twice daily | 1 capsule of 30 mg once daily |
| More than 15 kg and up to 23 kg | 1 capsule of 45 mg twice daily | 1 capsule of 45 mg once daily |
| More than 23 kg and up to 40 kg | 2 capsules of 30 mg twice daily | 2 capsules of 30 mg once daily |

*Children weighing more than 40 kg may receive medication with the adult dosage of Tamiflu 75 mg capsules twice daily for 5 days for treatment and once daily for 10 days for prevention.

2. Check that the correct dose according to the table above is used. The capsule(s) must be held over a small bowl, carefully pulled open and the powder poured into the bowl.
3. A suitable, small amount (1 teaspoon (5 mℓ) maximum) of sweetened food product must be added to the bowl (to mask the bitter taste) and the contents well mixed.

4. The mixture must be stirred and the entire contents of the bowl given to the patient.

   This mixture must be swallowed by the patient immediately after its preparation. If there is some mixture left inside the bowl, the bowl must be rinsed with a small amount of water and the patient must drink this remaining mixture.

*When using the 75 mg capsules*: for patients requiring 30 - 60 mg doses, follow these instructions to ensure proper dosing:

1. One Tamiflu 75 mg capsule must be held over a small bowl, the capsule must be carefully pulled open and the powder poured into the bowl.
2. 5 mℓ water must be added to the powder using a graduated syringe and the mixture stirred for approximately two minutes.
3. The correct amount of mixture must be drawn up into the syringe from the bowl. See the table below to determine the correct amount of mixture, based on the patient's weight. It is not necessary to draw up any undissolved white powder as this is inert material. The plunger of the syringe must be pushed down to empty its entire contents into a second bowl and any unused mixture discarded.

| ***Body Weight*** | ***Recommended dose*** | ***Required amount of Tamiflu mixture for one dose*** |
|---|---|---|
| Less than or equal to 15 kg | 30 mg | 2 mℓ |
| More than 15 kg and up to 23 kg | 45 mg | 3 mℓ |
| More than 23 kg and up to 40 kg | 60 mg | 4 mℓ |

4. The recommended dose is 30 mg, 45 mg or 60 mg twice daily for 5 days for treatment, and once daily for prevention for 10 days.
5. In the second bowl, a suitable, small amount (1 teaspoon (5 mℓ) maximum) of sweetened food product must be added to the mixture (to mask the bitter taste) and well mixed.
6. This mixture must be stirred and the entire contents of the second bowl given to the patient. This mixture must be swallowed immediately after its preparation. If there is some mixture

left inside the bowl, the bowl must be rinsed with a small amount of water and the patient must drink this remaining mixture.

For patients requiring 75 mg dose, follow these instructions:

1. One 75 mg capsule must be held over a small bowl, the capsule must be carefully pulled open and the powder poured into the bowl.
2. A suitable, small amount (1 teaspoon (5 mℓ) maximum) of sweetened food product must be added to the mixture (to mask the bitter taste) and well mixed.
3. The mixture must be stirred and the entire contents of the bowl given to the patient. This mixture must be swallowed immediately after its preparation. If there is some mixture left inside the bowl, it must be rinsed with a small amount of water and the patient must drink this remaining mixture.

**Repeat this procedure every time this medicine is taken.**

## SIDE EFFECTS

### Clinical Trials

The overall safety profile of Tamiflu is based on data from 2 647 adult/adolescent and 858 paediatric patients with influenza, and on data from 1 945 adult/adolescent and 148 paediatric patients receiving Tamiflu for the prophylaxis of influenza in clinical trials. In adult/adolescent treatment studies, the most frequently reported adverse drug reactions (ADRs) were nausea, vomiting and headache. The majority of reported ADRs occurred on either the first or second treatment day and resolved spontaneously within 1 - 2 days. In adult/adolescent prophylaxis studies, the most frequently reported ADRs were nausea, vomiting, headache and pain. In children, the most commonly reported ADR was vomiting.

***Treatment and prophylaxis of influenza in adults and adolescents***

In adult/adolescent treatment and prophylaxis studies, ADRs that occurred the most frequently (≥ 1 %) at the recommended dose (75 mg twice daily for 5 days for treatment and 75 mg once

daily for up to 6 weeks for prophylaxis), and whose incidence is at least 1 % higher on Tamiflu compared to placebo, are shown in the Table below.

The population included in the influenza treatment studies comprised of otherwise healthy adults/adolescents and patients “at risk” (patients at higher risk of developing complications associated with influenza, e.g. elderly patients and patients with chronic cardiac or respiratory disease). In general, the safety profile in the patients “at risk” was qualitatively similar to that in otherwise healthy adults/adolescents.

The safety profile reported in the subjects that received the recommended dose of Tamiflu for prophylaxis (75 mg once daily for up to 6 weeks) was qualitatively similar to that seen in treatment studies, despite a longer duration of dosing in the prophylaxis studies.

*Percentage of patients with ADRs that occurred in ≥ 1 % of the adults and adolescents in the Tamiflu group in studies investigating Tamiflu for treatment or prophylaxis of influenza:*

*Frequency categories: Very common (≥1/10); Common (≥1/100 and <1/10); Uncommon (≥1/1 000 and < 1/100); Rare (≥1/10 000 and <1/1 000); Very rare (≥1/10 000);*

| ***System Organ Class (SOC)*** **Adverse Drug Reaction** | **Frequency Category** | ***Treatment studies*** | | ***Prophylaxis studies*** | |
|---|---|---|---|---|---|
| | | Tamiflu (75 mg twice daily) N = 2 647 | Placebo N = 1 977 | Tamiflu (75 mg once daily) N = 1 945 | Placebo N = 1 588 |
| *Nervous system disorders* | | | | | |
| Headache | Very common | 2 % | 1 % | 17 % | 16 % |
| *Gastrointestinal disorders* | | | | | |
| Nausea | Very Common | 10 % | 6 % | 8 % | 4 % |
| Vomiting | Common | 8 % | 3 % | 2 % | 1 % |

| | | | | | |
|---|---|---|---|---|---|
| *General disorders*<br>Pain | Common | < 1 % | < 1 % | 4 % | 3 % |

Adverse events reported in ≥ 1 % of the adults and adolescents taking Tamiflu in the treatment studies (N = 2 647) and in the prophylaxis studies (N = 1 945), however which occurred more frequently in the patients on placebo or where the difference between the Tamiflu and placebo arm was < 1 %, were the following:

- *Infections and infestations*:
  - Treatment: bronchitis, sinusitis, herpes simplex
  - Prophylaxis: nasopharyngitis, upper respiratory tract infections, influenza
- *Nervous system disorders:*
  - Treatment: insomnia
  - Prophylaxis: insomnia
- *Respiratory, thoracic and mediastinal disorders*:
  - Treatment: cough, nasal congestion
  - Prophylaxis: nasal congestion, sore throat, cough, rhinorrhoea
- *Gastrointestinal disorders*:
  - Treatment: diarrhoea, abdominal pain (including upper abdominal pain)
  - Prophylaxis: diarrhoea, upper abdominal pain, dyspepsia
- *Musculoskeletal, connective tissue and bone disorders*:
  - Prophylaxis: back pain, arthralgia, myalgia
- *Reproductive system and breast disorders*:
  - Prophylaxis: dysmenorrhoea
- *General disorders*:
  - Treatment: dizziness (including vertigo)
  - Prophylaxis: fatigue, pyrexia, influenza-like illness, dizziness, pain in limb

***Treatment and prophylaxis of influenza in the elderly***

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.

***Prophylaxis of influenza in immuno-compromised subjects***

In a 12-week prophylaxis study in 475 immuno-compromised subjects, including 18 children 1 - 12 years of age, the safety profile in the 238 subjects receiving Tamiflu was consistent with that previously observed in Tamiflu prophylaxis clinical trials.

***Treatment and prophylaxis of influenza in children***

A total of 1 480 children aged 1 - 12 years (including 698 otherwise healthy children aged 1 - 12 and 334 asthmatic children aged 6 - 12) participated in phase III studies of Tamiflu given for the treatment of influenza. A total of 858 children received treatment with Tamiflu suspension.

The ADRs that occurred in ≥ 1 % of children aged 1 to 12 years receiving Tamiflu in clinical trials for treatment of naturally acquired influenza (N = 858), and whose incidence is at least 1 % higher on Tamiflu compared to placebo (N = 622), is vomiting (16 % on Tamiflu vs. 8 % on placebo). Amongst the 148 children who received the recommended dose of Tamiflu once daily in a post-exposure prophylaxis study in households (N = 99), and in a separate 6-week paediatric prophylaxis study (N = 49), vomiting was the most frequent ADR (8 % on Tamiflu vs. 2 % in the no prophylaxis group). The adverse events noted were consistent with those previously observed in paediatric treatment studies.

Adverse events reported in ≥ 1 % of the children taking Tamiflu in the treatment studies (N = 858) or ≥ 5 % of the children in the prophylaxis studies (N = 148), were the following:

- *Infections and infestations*:
  - Treatment: otitis media, bronchitis, pneumonia, sinusitis
- *Eye disorders*:
  - Treatment: conjunctivitis (including red eyes, eye discharge and eye pain)
- *Ear and labyrinth disorders*:
  - Treatment: earache

- *Respiratory, thoracic and mediastinal disorders*:
  - Treatment: asthma (including aggravated asthma), epistaxis
  - Prophylaxis: cough, nasal congestion
- *Gastrointestinal disorders*:
  - Treatment: diarrhoea, nausea, abdominal pain (including upper abdominal pain)
- *Skin and subcutaneous tissue disorders*:
  - Treatment: dermatitis (including allergic and atopic dermatitis)

Additional adverse events reported from paediatric treatment studies, which previously qualified to be presented above, however in larger datasets did not fulfil the criteria for inclusion in previous sections anymore, are given below:

- *Blood and lymphatic system disorders*:
  - Treatment: lymphadenopathy
- *Ear and labyrinth disorders*:
  - Treatment: tympanic membrane disorder

***Observational data in infants under 1 year of age***

Safety information available on Tamiflu administered for treatment of influenza in infants less than 1 year of age from prospective and retrospective observational trials (comprising together more than 2 400 children of that age class), epidemiological database research and post-marketing reports suggest that the safety profile in children less than 1 year of age is similar to the established safety profile of children aged 1 year and above.

*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 in the age group 1 to 12 years of age.

**Post-Marketing Experience**

*Psychiatric disorders/Nervous system disorders:* Neuropsychiatric events such as convulsions, abnormal and inappropriate behaviour, including abnormal motor behaviour, disturbances in consciousness, hallucinations and delirium have been reported. In some cases, the delirium resulted in accidental self-injury and death. More events were reported in males than in females. These neuropsychiatric events occurred mostly within the first few days of administration of Tamiflu. Patients, especially paediatric and adolescent patients should therefore be carefully monitored for abnormal behaviour for the first few days. Convulsions and psychiatric symptoms have also been reported in patients with influenza who were not taking Tamiflu.

*Immune system disorders:* allergy, anaphylactic/anaphylactoid reactions and face oedema have been reported.

*Skin and subcutaneous tissue disorders*: Cases of hypersensitivity reactions such as allergic skin reactions including dermatitis, rash, eczema, urticaria, erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis have been reported.

*Hepato-biliary disorders:* Hepatitis and elevated liver enzymes have been reported in patients with influenza-like illness receiving Tamiflu.

*Gastrointestinal disorders:* Gastrointestinal bleedings, in particular, haemorrhagic colitis was reported that subsided when the course of influenza abated or treatment with Tamiflu was interrupted.

## KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In overdose, symptoms may be the exacerbation or exaggeration of side effects.

Treatment is supportive and symptomatic.

## IDENTIFICATION

**Tamiflu 30 mg Capsules**: Light yellow opaque hard gelatin capsules. "ROCHE" and "30 mg" is printed in blue ink.

**Tamiflu 45 mg Capsules**: Grey opaque hard gelatin capsules. "ROCHE" and "45 mg" is printed in blue ink.

**Tamiflu 75 mg Capsules**: Grey/light yellow opaque 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 opaque cap.

**Tamiflu 6 mg/mℓ** Powder for Oral Suspension: White to light yellow granules. After reconstituting the 13 g of Tamiflu Powder for Oral suspension with 55 mℓ of water it will appear as a white to light yellow, opaque suspension.

## PRESENTATION

**Tamiflu 30 mg, 45 mg & 75 mg** Capsules: Boxes containing 10 capsules in blister pack. Blister packs are composed of transparent plastic (PVC/PE/PVDC) and aluminium foil.

**Tamiflu 6 mg/mℓ:** Powder for Oral Suspension: Carton containing a 100 mℓ amber glass bottle with a child-resistant white polypropylene plastic screw cap, a press-in oral adapter and a 10 mℓ plastic oral dispenser (transparent polypropylene barrel with a white polypropylene plunger). After reconstitution with 55 mℓ of water, the usable volume of oral suspension allows for the retrieval of a total of 10 doses of 60 mg oseltamivir.

## STORAGE INSTRUCTIONS

**Tamiflu 30 mg, 45 mg & 75 mg** Capsules

Do not store above 25 °C. Protect from light. Keep blisters in outer carton until required for use.

Store out of reach of children.

Do not use Tamiflu 30 mg, 45 mg & 75 mg Capsules after the expiry date shown on the box.

**Tamiflu 6 mg/mℓ** Powder for Oral Suspension

Store at or below 25 °C. Protect from light. Keep bottle tightly closed.

After reconstitution, store the suspension below 25 °C and use within 10 days or at 2 °C - 8 °C (in a refrigerator) and use within 17 days.

Shake the reconstituted suspension well before use.

Store all medicines out of reach of children.

## REGISTRATION NUMBERS

**Tamiflu 30 mg** Capsules: 42/20.2.8/1020

**Tamiflu 45 mg** Capsules: 42/20.2.8/1021

**Tamiflu 75 mg** Capsules: A40/20.2.8/0578

**Tamiflu 6 mg/mℓ** Powder for Oral Suspension: 47/20.2.8/1194

## NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

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Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

## DATE OF PUBLICATION OF THE PACKAGE INSERT

Registration: 75 mg capsules – 17 Feb 2006

30 mg and 45 mg capsules – 26 Nov 2010

6mg/mℓ powder for oral suspension: 11 Jun 2018

Last revision: 22 July 2022

## Registration number(s)

| | |
|---|---|
| **Tamiflu® 75 mg** | Botswana: S2 BOT0901570 |
| | Namibia: NS2 06/20.2.8/0322 |
| | Zimbabwe: PP 2003/7.13/4176 |
| **Tamiflu® 6 mg/mL** | Botswana: S2 BOT2203805 |
| | Namibia: NS2 18/20.2.8/0078 |

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