PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

Tamiflu® 30 mg Capsules

Tamiflu® 45 mg Capsules

Tamiflu® 75 mg Capsules

Tamiflu® 6 mg/mL Powder for Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tamiflu contains oseltamivir as the active substance.

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

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

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

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.

For the full list of excipients, see section 6.1.

Excipients with known effect:

Tamiflu Powder for Oral Suspension

Contains sugar (sorbitol).

5 mL oseltamivir suspension delivers 0.9 g of sorbitol and 2.5 mg of sodium benzoate.

7.5 mL oseltamivir suspension delivers 1.3 g of sorbitol and 3.75 mg of sodium benzoate.

10 mL oseltamivir suspension delivers 1.7 g of sorbitol and 5.0 mg of sodium benzoate.

12.5 mL oseltamivir suspension delivers 2.1 g of sorbitol and 6.25 mg of sodium benzoate.

Tamiflu 30 mg Capsules:

Sugar free

Colourants: The capsule shell contains yellow iron oxide (E172), red iron oxide (E172) and titanium dioxide (E171). The printing ink contains traces of titanium dioxide (E171) and FD and C Blue 2 (Indigo carmine, E132).

Tamiflu 45 mg Capsules

Sugar free

Contains colourants: The capsule shell contains black iron oxide (E172) and titanium dioxide (E171). The printing ink contains traces of titanium dioxide (E171) and FD and C Blue 2 (Indigo carmine, E132).

Tamiflu 75 mg Capsules

Sugar free

Contains colourants: The capsule shell contains black iron oxide (E172), yellow iron oxide (E172), red iron oxide (E172) and titanium dioxide (E171). The printing ink contains traces of titanium dioxide (E171) and FD and C Blue 2 (Indigo carmine, E132)

3 PHARMACEUTICAL FORM

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.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of Influenza

Tamiflu is indicated for the treatment of influenza in adults and children including full-term neonates who present with symptoms typical of influenza, when influenza virus is circulating in the community. Efficacy has been demonstrated when treatment is initiated within the two days of first onset of symptoms (see Section 4.2 and 4.4).

Prophylaxis of Influenza

Tamiflu is indicated for the prophylaxis of influenza in adults and children ≥ 1 year of age following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

Tamiflu is indicated for the prophylaxis of influenza in infants less than 1 year of age during a pandemic influenza outbreak.

Tamiflu is not a vaccine.

4.2 Posology and method of administration

General

Tamiflu may be taken with or without food (see section 5.2). However, Tamiflu taken with food may enhance tolerability in some patients.

Posology

Treatment of influenza

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

Efficacy has not been established in patients who begin treatment after 2 days of symptoms.

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 for 5 days:

Body weight	***Recommended dose for 5 days***	
	Capsules	***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 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 <1 year of age:

The recommended oral dose of Tamiflu for children 0 to 12 months is 3 mg/kg twice daily, for 5 days. These dosing recommendations are not intended for infants who have a post-conceptual age of less than 36 weeks.

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

Body Weight (kg)	***Tamiflu (mg) Recommended dose for 5 days***	***Amount of 6 mg/mL suspension***
3 kg	9 mg twice daily	1,5 mL twice daily
4 kg	12 mg twice daily	2,0 mL twice daily
5 kg	15 mg twice daily	2,5 mL twice daily
6 kg	18 mg twice daily	3,0 mL twice daily
7 kg	21 mg twice daily	3,5 mL twice daily
8 kg	24 mg twice daily	4,0 mL twice daily
9 kg	27 mg twice daily	4,5 mL twice daily
≥ 10 kg	30 mg twice daily	5,0 mL twice daily

* This table is not intended to contain all possible weights for this population. For all patients under the age of 1 year of age, 3 mg/kg should be used to determine dose regardless of the weight of the patient.

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.

Efficacy has not been established in patients who begin treatment after 2 days of symptoms.

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 10 days:

Body Weight	***Recommended dose for 10 days***	
	Capsules	***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 *Section 6.6*).

Special Populations

Geriatric use

No dose adjustment is required for elderly patients in the treatment or prophylaxis of influenza (see section 5.2).

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 section 4.4 and 5.2). 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 section 4.4 and 5.2) 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 section 5.2). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Immuno-compromised patients

Treatment of Influenza

The recommended duration for immunocompromised patients is 10 days. No dose adjustment is necessary.

Prophylaxis of Influenza

Seasonal prophylaxis in immuno-compromised patients 1 year of age and older is recommended for 12 weeks. No dose adjustment is necessary *(see “Prophylaxis of Influenza”).*

Paediatric Population

The efficacy of Tamiflu in children under 1 year has not been established (see section 5.2). Pharmacokinetic data indicate~~s~~ that a dosage of 3 mg/kg twice daily in children 0 – 12 months

of age provides plasma concentrations of the pro-drug and active metabolite that are anticipated to be clinically efficacious with a safety profile comparable to that seen in older children and adults (See section 4.1).

Method of administration

Oral use.

Patients who are unable to swallow capsules may receive appropriate doses of Tamiflu suspension.

4.3 Contraindications

Tamiflu is contraindicated in patients with known hypersensitivity to oseltamivir phosphate or to any component of Tamiflu (see section 6.1).

4.4 Special warnings and precautions for use

General

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

Resistance of influenza viruses to Tamiflu has 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.

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 section 4.2).

Sugars

Tamiflu Powder for Oral Suspension contains sorbitol which may have a laxative effect. Patients with the rare hereditary condition of sorbitol intolerance should not take Tamiflu Powder for Oral Suspension.

Sodium benzoate

The medicine contains sodium benzoate. Sodium benzoate (E211) may increase jaundice in newborn babies (up to 4 weeks old).

4.5 Interaction with other medicines and other forms of interaction

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 section 5.2).
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), H2-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.

4.6 Fertility, pregnancy and lactation

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; however, there is evidence from post-marketing and observational studies showing benefit of the current dosing regimen in this patient population. Results from pharmacokinetic analyses indicate a lower exposure to the active metabolite, however dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section 5.2 Pharmacokinetics in Special Population). Data from pregnant women exposed to Tamiflu (more than 1 000 exposed outcomes during the first trimester) from post-marketing reports and observational studies in conjunction with animal studies indicate no direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development. Pregnant women may receive Tamiflu, after considering the available safety and benefit information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

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; however, the levels were low, which would result in a sub-therapeutic dose to the infant. Based on this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the lactating woman, administration of Tamiflu could be considered.

Fertility

Fertility studies have been conducted in rats. There is no evidence of an effect on male and female fertility at any dose of oseltamivir studied.

4.7 Effects on ability to drive and use machines

Tamiflu has negligible or no influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile:

The overall safety profile of Tamiflu is based on data from 2646 adult/adolescent, 859 paediatric patients with influenza, 1943 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. In the majority of patients, these events did not lead to discontinuation of Tamiflu.

b. Tabulated list of adverse reactions

Treatment and prophylaxis of influenza in adults and adolescents

In adult/adolescent treatment and prophylaxis studies, ADRs that occurred 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 was at least 1 % higher on Tamiflu compared to placebo

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.
Adverse drug reactions from clinical trials are listed according to the MedDRA system organ class. The corresponding frequency category for each adverse drug reaction (Table 1) is based on the following convention:

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).

Table 1: Adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Bronchitis, Herpes simplex, Nasopharyngitis, Upper respiratory tract infections, Sinusitis		
Blood and lymphatic system disorders				Thrombocytopenia
Immune system disorders			Hypersensitivity reaction	Anaphylactic reactions, Anaphylactoid reactions
Psychiatric disorders				Agitation, Abnormal behaviour, Anxiety, Confusion, Delusions, Delirium, Hallucination, Nightmares, Self-injury
Nervous system disorders	Headache	Insomnia	Altered level of consciousness, Convulsion	
Eye disorders				Visual disturbance
Cardiac disorders			Cardiac dysrhythmia	
Respiratory, thoracic and mediastinal disorders		Cough, Sore throat, Rhinorrhea		
Gastrointestinal disorders	Nausea	Vomiting Abdominal pain (incl. upper abdominal pain), Dyspepsia		Gastrointestinal bleedings, Haemorrhagic colitis
Hepatobiliary disorders			Elevated liver enzymes	Fulminant hepatitis, Hepatic failure, Hepatitis
Skin and subcutaneous tissue disorders			Eczema, Dermatitis, Rash, Urticaria	Angioneurotic oedema, Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis
General disorders and administration site conditions		Pain Dizziness (incl. vertigo), Fatigue, Pyrexia, Pain in limb		

Treatment and prophylaxis of influenza in children ≥ 1 year of age

A total of 1 481 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 859 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 = 859), and whose incidence was at least 1 % higher on Tamiflu compared to placebo (N = 622), was 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.

Treatment and prophylaxis of Influenza in Children under 1 Year of Age

In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of oseltamivir therapy in 124 influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrhoea and diaper rash being the most frequently reported AEs (see section 5.2). Insufficient data are available for infants who have a post conceptual age of less than 36 weeks.

Safety information available on Tamiflu administered for treatment of influenza in children less than 1 year of age from prospective and retrospective observational trials (comprising together more than 2400 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.

Treatment and prophylaxis of influenza in **Geriatric patients**

There were no clinically relevant differences in the safety profile of the 942 elderly subjects (65 years of age and older), who received Tamiflu or placebo, compared with the younger population (aged up to 65 years).

Treatment and Prophylaxis of influenza in immuno-compromised subjects

The treatment of influenza in immunocompromised patients were evaluated in two studies receiving standard dose or high dose regimens (double dose or triple dose) of Tamiflu. The safety profile of Tamiflu observed in these studies was consistent with that observed in previous clinical trials where Tamiflu was administered for the treatment of influenza in non-immunocompromised patients across all age groups (otherwise healthy patients or “at risk” patients [i.e., those with respiratory and/or cardiac co-morbidities]). The most frequent ADR reported in immunocompromised children was vomiting (28 %).

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.

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 of treatment.

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 has been reported and subsided when the course of influenza abated or treatment with Tamiflu was interrupted.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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

Reports of overdoses with Tamiflu have been received from clinical trials and during post-marketing experience. In the majority of cases reporting overdose, no adverse events were reported.

Adverse events reported following overdose were similar in nature and distribution to those observed with therapeutic doses of Tamiflu (see section 4.8).

Treatment is supportive and symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral agents, ATC code: J05AH02

Mechanism of action

Oseltamivir phosphate is a pro-drug and selective inhibitor of influenza virus neuraminidase enzymes. Viral neuraminidase is primarily essential for the release of recently formed virus particles from infected cells, and the further spread of infectious virus. It has also been suggested that neuraminidase can play a role in viral entry into uninfected cells.

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.

Oseltamivir resistance

For information on resistance in South Africa, please refer to section 4.4, sub-section ‘Resistance’.

Clinical studies: The risk of emergence of influenza viruses with reduced susceptibility or frank resistance to oseltamivir has been examined during Roche-sponsored clinical studies.

Developing oseltamivir-resistant virus during treatment was more frequent in children than adults, ranging from less than 1% in adults to 18% in infants aged below 1 year. Children who were found to carry oseltamivir-resistant virus in general shed the virus for a prolonged period compared with subjects with susceptible virus. However treatment-emergent resistance to oseltamivir did not affect treatment response and caused no prolongation of influenza symptoms.

An overall higher incidence of oseltamivir resistance was observed in adult and adolescent immunocompromised patients treated with standard dose or double dose of oseltamivir for a duration of 10 days [14.5% (10/69) in standard dose group and 2.7% (2/74) in double dose group], compared to data from studies with oseltamivir-treated otherwise healthy adult and adolescent patients. The majority of adult patients that developed resistance were transplant recipients (8/10 patients in the standard dose group and 2/2 patients in the double dose group). Most of the patients with oseltamivir-resistant virus were infected with influenza type A and had prolonged viral shedding.

The incidence of oseltamivir-resistance observed in immunocompromised children (≤12 years of age) treated with Tamiflu across the two studies and evaluated for resistance was 20.7% (6/29). Of the six immunocompromised children found with treatment-emergent resistance to oseltamivir, 3 patients received standard dose and 3 patients high dose (double or triple dose). The majority had acute lymphoid leukemia and were ≤ 5 years of age.

Incidence of Oseltamivir Resistance in Clinical Studies

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	Geno- and Phenotyping*
Adults and adolescents	0.88% (21/2382)	1.13% (27/2396)

Children (1-12 years)	4.11% (71/1726)	4.52% (78/1727)
Infant (<1 year)	18.31% (13/71)	18.31 (13/71)

* Full genotyping was not performed in all studies.

Prophylaxis of Influenza

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

Clinical and surveillance data: Natural mutations associated with reduced susceptibility to oseltamivir in vitro have been detected in influenza A and B viruses isolated from patients without exposure to oseltamivir. For example, in 2008 the oseltamivir resistance-associated substitution H275Y was found in > 99% of circulating 2008 H1N1 influenza isolates in Europe, while the 2009 H1N1 influenza (“swine flu”) was almost uniformly susceptible to oseltamivir. Resistant strains have also been isolated from both immunocompetent and immunocompromised patients treated with oseltamivir. The susceptibility to oseltamivir and the prevalence of such viruses appears to vary seasonally and geographically. Oseltamivir resistance has also been reported in patients with pandemic H1N1 influenza in connection with both therapeutic and prophylactic regimens.

The rate of emergence of resistance may be higher in the youngest age groups, and in immunocompromised patients. Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivir-resistant laboratory strains of influenza viruses have been found to contain mutations in N1 and N2 neuraminidases. Resistance mutations tend to be viral sub-type specific.

5.2 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 (oseltamivir carboxylate). Plasma concentrations of the active metabolite are measurable within 30 minutes following ingestion of oseltamivir, 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 section 4.2).

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 its 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 section 4.5).

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 metabolite 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

Paediatric population

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.

Children <1 year of age

The pharmacokinetics, pharmacodynamics and safety of oseltamivir have been evaluated in two open-label studies including influenza infected children less than one year of age (n=124). The available data indicates that the exposure following a 3 mg/kg dose in most children 0 – 12 months of age provides pro-drug and metabolite exposures anticipated to be efficacious

with a safety profile comparable to that seen in older children and adults using the approved dose. The reported adverse events were consistent with the established safety profile in older children.

Geriatric population

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, unless there is evidence of moderate to severe renal impairment (see section 4.2).

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 (see section 4.2).

Hepatic impairment

In-vitro studies have shown that exposure to oseltamivir is not expected to be increased significantly nor is exposure to its active metabolite expected to be significantly decreased in patients with mild or moderate hepatic impairment (see section 4.2). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Immunocompromised Patients

Population pharmacokinetic analyses indicates that treatment of adult and paediatric (<18 years old) immunocompromised patients with oseltamivir (Section 4.2) results in an increased exposure (of up to 50 %) to the active metabolite when compared to non-immunocompromised

patients. However, due to the wide safety margin of the active metabolite, no dose adjustments are required in immunocompromised patients in the absence of renal impairment.

Pharmacokinetic and pharmacodynamic analyses from two studies in IC patients indicated that there was no meaningful additional benefit in exposures higher than those achieved after the administration of the standard dose.

Pregnant Women

A pooled population pharmacokinetic analysis indicated that the oseltamivir dosage regimen (Section 4.2) results in lower exposure (30 % on average across all trimesters) to the active metabolite in pregnant women compared to non-pregnant women. The lower predicted exposure however, remains above inhibitory concentrations (IC_{95} values) and at a therapeutic level for a range of influenza virus strains. In addition, there is evidence from observational studies showing benefit of the current dosing regimen in this patient population. Therefore, dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tamiflu 30 mg Capsules

Povidone, pregelatinised starch, 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

Black iron oxide (E172), gelatin 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

Povidone, pregelatinised starch, 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

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Capsules

Do not store above 25 °C: up to 120 months shelf life.

Powder for oral suspension

Do not store above 25 °C: up to 24 months shelf life.

6.4 Special precautions for storage

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 and 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.

6.5 Nature and contents of container

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 is 64,7 mL.

6.6 Special Instructions for Use, Handling and Disposal

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.

Instructions for use and handling

Commercially manufactured Tamiflu for oral suspension (6 mg/mL) is the preferred product for paediatric and adult patients who have difficulty swallowing capsules or where lower doses are needed. In the event that Tamiflu for oral suspension is not available, the pharmacist may compound a suspension (6 mg/mL) from Tamiflu capsules.

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.

Emergency Compounding of an Oral Suspension from Tamiflu Capsules (Final Concentration 6 mg/mL).

Preparation of the pharmacy-compounded suspension (6 mg/mL)

This procedure describes the preparation of a 6 mg/mL suspension that will provide one patient with enough medication for a 5–day course of treatment.

The pharmacist may compound a suspension (6 mg/mL) from Tamiflu 30 mg, 45 mg or 75 mg capsules using water containing 0,05 % w/v sodium benzoate added as a preservative.

First, calculate the Total Volume needed to be compounded and dispensed for each patient. The Total Volume required is determined by the weight of the patient according to the recommendation in the table below:

Volume of Pharmacy Compounded Suspension (6 mg/mL) required for a 5-day course based upon the patient's weight

Body Weight (kg)	**Total Volume to Compound (mL)**
up to 5 kg	25 mL
> 5 to 6 kg	30 mL
> 6 to 15 kg	50 mL
> 15 to 23 kg	75 mL
> 23 to 40 kg	100 mL
> 40 kg	125 mL

Second, determine the number of capsules and the amount of vehicle (water containing 0,05 % w/v sodium benzoate added as a preservative) that is needed to prepare the Total Volume

(calculated from the table above: 25 mL, 30 mL, 50 mL, 75 mL, 100 mL, or 125 mL) of pharmacy compounded suspension (6 mg/mL) as shown in the table below:

Number of capsules and amount of vehicle needed to prepare the total volume of a Pharmacy Compounded Suspension (6 mg/mL)

Total Volume of Compounded Suspension to be Prepared	**Required Number of Tamiflu Capsules (mg of oseltamivir)**			**Required Volume of Vehicle**
	75 mg	**45 mg**	**30 mg**	
25 mL	2 capsules (150 mg)	Please use alternative capsule strength*	5 capsules (150 mg)	24,5 mL
30 mL	Please use alternative capsule strength*	4 capsules (180 mg)	6 capsules (180 mg)	29,5 mL
50 mL	4 capsules (300 mg)	Please use alternative capsule strength*	10 capsules (300 mg)	49,5 mL
60 mL	Please use alternative capsule strength*	8 capsules (360 mg)	12 capsules (360 mg)	59 mL
75 mL	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	74 mL

Total Volume of Compounded Suspension to be Prepared	**Required Number of Tamiflu Capsules (mg of oseltamivir)**			**Required Volume of Vehicle**
	75 mg	**45 mg**	**30 mg**	
90 mL	Please use alternative capsule strength*	12 capsules (540 mg)	18 capsules (540 mg)	89 mL
100 mL	8 capsules (600 mg)	Please use alternative capsule strength*	20 capsules (600 mg)	98,5 mL
120 mL	Please use alternative capsule strength*	16 capsules (720 mg)	Please use alternative capsule strength*	118,5 mL
125 mL	10 capsules (750 mg)	Please use alternative capsule strength*	Please use alternative capsule strength*	123,5 mL

*No integral number of capsules can be used to achieve the target concentration; therefore, please use an alternate capsule strength.

Third, follow the procedure below for compounding the suspension (6 mg/mL) from Tamiflu capsules:

1. Transfer the contents of the stated amount of Tamiflu capsules into the bottle and add the stated amount of sodium benzoate solution (Table above).
2. Close the bottle with the cap and shake for two minutes.
3. Put an ancillary label on the bottle indicating “Shake Gently Before Use”.

4. Instruct the parent or caregiver to discard any remaining solution after the patient has completed the full course of therapy.

5. Place an appropriate expiration date label according to storage condition (see below).

Storage of the pharmacy-compounded suspension (6 mg/mL)

Room temperature storage conditions: Stable for 3 weeks (21 days) when stored at or below 25 °C.

Refrigerated storage conditions: Stable for 6 weeks when stored at 2°C–8°C.

Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, use by date, product name and any other required information to be in compliance with local pharmacy regulations.

Dosing of the pharmacy-compounded suspension (6 mg/mL)

Refer to section 4.2 above for the proper dosing instructions.

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.

The suspension must be dispensed with a graduated oral syringe for measuring small amounts of suspension.

Emergency Home Preparation of an Oral Suspension from Tamiflu Capsules

If the commercially manufactured Tamiflu oral suspension (6 mg/mL) is not available and the pharmacy compounded suspension is also not available, Tamiflu suspension may be prepared at home if directed by the healthcare provider.

When appropriated capsule strengths are available for the dose needed (75 mg, 45 mg and 30 mg), the dose is given by opening the capsule and mixing its contents with no more than

one teaspoon of a suitable sweetened food product (e.g. chocolate syrup, cherry syrup, sugar water, dessert toppings). The mixture should be stirred and given entirely to the patient.

The mixture must be swallowed immediately after its preparation.

When only 75 mg capsules are available, and doses of 30 mg or 45 mg are needed, and or for younger children and infants who may need a Tamiflu dose <30 mg, the home preparation of the Tamiflu suspension involves additional steps. Instructions for home preparation and syringes of appropriate volume and grading can be requested from the health care provider, such as the pharmacist. Refer for section 4.2.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley, Midrand

Johannesburg, 1686

South Africa

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

8. REGISTRATION NUMBER

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of 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

10. DATE OF REVISION OF THE TEXT

Last revision: 19 February 2025

Registration number(s)

Tamiflu® 75 mg	Botswana: S2 BOT0901570
	Namibia: NS2 06/20.2.8/0322
Tamiflu® 6 mg/mL	Botswana: S2 BOT2203805
	Namibia: NS2 18/20.2.8/0078

Approved manufacturer(s):

Tamiflu 75 mg

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Tamiflu 6 mg/mL

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