TAMIFLU
Oseltamivir

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1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Tamiflu is an anti-viral agent

ATC: J05AH02

1.2 TYPE OF DOSAGE FORM

Capsule, hard

30 mg capsule consisting of a light yellow opaque body bearing the imprint “ROCHE” and a light yellow opaque cap bearing the imprint “30 mg”. Imprints are blue.

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

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

Powder for oral suspension.

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

1.3 ROUTE OF ADMINISTRATION

Oral

1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: oseltamivir phosphate.

30 mg capsules, containing 39.4 mg oseltamivir phosphate equivalent to 30 mg of oseltamivir.

45 mg capsules, containing 59.1 mg oseltamivir phosphate equivalent to 45 mg of oseltamivir.

75 mg capsules, containing 98.5 mg oseltamivir phosphate equivalent to 75 mg of oseltamivir.

Powder for oral suspension, which when constituted with water to a concentration of 0.6% contains 6 mg/mL oseltamivir

List of Excipients

Excipients: described as per local requirements.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Tamiflu is indicated for the treatment of influenza in adults and children including full-term neonates (see sections 2.2.1 Special Dosage Instruction, 2.4 Warnings and Precautions and 3.3 Nonclinical Safety).

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

2.2 DOSAGE AND ADMINISTRATION

Tamiflu may be taken with or without food (see section 3.2 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 75 mg twice daily, for 5 days. Adults and adolescents ≥ 13 years of age that are unable to swallow capsules may receive a dose of 75 mg Tamiflu suspension b.i.d. 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 suspension.

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

Body weight	Recommended dose for 5 days	Amount of Oral Suspension (6mg/mL)
≤ 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

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	Recommended dose for 5 days	Amount of Oral Suspension (6mg/mL)
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
9kg	27 mg twice daily	4.5 mL twice daily

10kg	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, 3mg/kg should be used to determine dose regardless of the weight of the patient.

It is recommended that Tamiflu powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient (see section 4.2 Special Instructions for Use).

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 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 suspension.

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

Body weight	Recommended dose for 10 days	Amount of Oral Suspension (6 mg/mL)
≤ 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

It is recommended that Tamiflu powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient (see section 4.2 Special Instructions for Use, Handling and Disposal).

2.2.1 Special Dosage Instructions

Pediatric Use

The efficacy of Tamiflu in children less than one year of age has not been established (see section 3.2.5 Pharmacokinetics in Special Populations). Pharmacokinetic data indicates 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 2.1 Therapeutic Indications).

Geriatric Use

No dose adjustment is required for elderly patients in the treatment or prophylaxis of influenza (see section 3.2.5 Pharmacokinetics in Special Populations).

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 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 hemodialysis an initial dose of 30 mg of 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 hemodialysis session. For peritoneal dialysis a 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 sections 3.2.5 Pharmacokinetics in Special Populations and 2.4 Warnings and 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 Tamiflu once daily. In patients with 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 hemodialysis 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 hemodialysis 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 sections 3.2.5 Pharmacokinetics in Special Populations and 2.4 Warnings and 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

No dose adjustment is required for patients with mild or moderate hepatic dysfunction in the treatment or prophylaxis of influenza (see sections 3.2.5 Pharmacokinetics in Special Populations). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Immunocompromised Patients

Treatment of Influenza

The recommended duration for immunocompromised patients is 10 days. No dose adjustment is necessary (see Sections 2.6.1 and 3.1.2).

Prophylaxis of Influenza

Seasonal prophylaxis in immunocompromised patients 1 year of age and older is recommended for 12 weeks. No dose adjustment is necessary (see "Prophylaxis of Influenza" in section 2.2).

2.3 CONTRAINDICATIONS

Tamiflu is contraindicated in patients with known hypersensitivity to oseltamivir phosphate or to any component of the product.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

Convulsion and delirium-like neuropsychiatric events have been reported during Tamiflu administration in patients with influenza, predominately in children and adolescents. In rare cases, these events resulted in accidental injury. The contribution of Tamiflu to those events is unknown and these have also been reported in patients with influenza who were not taking Tamiflu. Three separate large epidemiological studies confirmed that influenza infected patients receiving Tamiflu are at no higher risk of developing neuropsychiatric events in comparison to influenza infected patients not receiving antivirals (see section 2.6.2 Post Marketing).

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

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

For dose adjustments in patients with renal impairment see section 2.2.1 Special Dosage Instructions (see also 3.2.5 Pharmacokinetics in Special Populations).

A bottle of 30 g Tamiflu powder for oral suspension contains 25.713 g of sorbitol. One dose of 45 mg oseltamivir administered twice daily delivers 2.6 g of sorbitol. For subjects with hereditary fructose intolerance this is above the recommended daily maximum limit of sorbitol.

2.4.2 Drug Abuse and Dependence

Not applicable.

2.4.3 Ability to Drive and Use Machines

No or negligible influence on the ability to drive and use machines.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females & Males of Reproductive Potential

Fertility

Fertility studies have been conducted in rats. There was no evidence of an effect on male or female fertility at any dose of oseltamivir studied. See section 3.3.3 Impairment of Fertility.

2.5.2 Pregnancy

Risks to the Developing Embryo/Fetus and to the Mother

In animal reproductive studies in rats and rabbits, no teratogenic effect was observed. Foetal exposure in rats and rabbits was approximately 15–20% of that of the mother.

No controlled clinical trials have been conducted on the use of oseltamivir 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 3.2.5 Pharmacokinetics in Special Population). A large amount of data from pregnant women exposed to oseltamivir (more than 1000 exposed outcomes during the first trimester) from post-marketing reports and observational studies in conjunction with animal studies (see section 3.3 Nonclinical Safety)

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.

Labor and Delivery

The safe use of oseltamivir during labor and delivery has not been established.

2.5.3 Lactation

In lactating rats, oseltamivir and the active metabolite are excreted in milk. Very limited information is available on children breast-fed by mothers taking oseltamivir and on excretion of oseltamivir in breast milk. Limited data demonstrated that 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 oseltamivir may be considered.

2.5.3 Paediatric Use

See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations

2.5.4 Geriatric Use

See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations

2.5.5 Renal Impairment

See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations

2.5.6 Hepatic Impairment

See sections 2.2.1 Special Dosage Instructions and 3.2.5 Pharmacokinetics in Special Populations

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

Summary of Safety Profile

The overall safety profile of Tamiflu is based on data from 2646 adult/adolescent and 859 paediatric patients with influenza, and on data from 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 these ADRs were reported on a single occasion, 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.

Tabulated summary of adverse drug reactions from clinical trials

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: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

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 b.i.d. for 5 days for treatment and 75 mg o.d. for up to 6 weeks for prophylaxis), and whose incidence is at least 1% higher on Tamiflu compared to placebo, are shown in Table 1.

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 the treatment studies (Table 1), despite a longer duration of dosing in the prophylaxis studies.

Table 1 Summary of Adverse Reactions in ≥ 1% of adult and adolescent patients that received oseltamivir for treatment or prophylaxis of influenza, in clinical studies (difference to placebo ≥ 1%) .

System Organ Class Adverse Drug Reaction	Treatment studies	Prophylaxis	Frequency category[a]
	Oseltamivir (75 mg b.i.d.) N = 2646	Oseltamivir (75 mg o.d.) N = 1943	
Gastrointestinal Disorders			
Nausea	10%	8%	very common
Vomiting	8%	2%	common
Nervous System Disorders			
Headache	2%	17%	very common
General Disorders			
Pain	<1%	4%	common

[a] Frequency category is reported only for the oseltamivir group.

Treatment and Prophylaxis of Influenza in Children ≥ 1 year of age

A total of 1481 children (including otherwise healthy children aged 1–12 and asthmatic children aged 6–12) participated in clinical studies of oseltamivir given for the treatment of influenza. A total of 859 children received treatment with oseltamivir suspension.

The ADR that occurred in ≥ 1% of children aged 1 to 12 years receiving oseltamivir in the clinical trials for treatment of naturally acquired influenza (n = 859), and whose incidence is at least 1% higher on Tamiflu compared to placebo (n = 622), is vomiting (16% on oseltamivir 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 oseltamivir vs. 2% in the no prophylaxis group). Tamiflu was well tolerated in these studies and the adverse events noted were consistent with those previously observed in paediatric treatment studies.

Data in Children under 1 Year of Age

In two studies to characterize 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, diarrhea and diaper rash being the most frequently reported AEs (see 3.2.5 Pharmacokinetics in Special Populations). 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 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 Immunocompromised 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 (see Section 3.1.2 Clinical/Efficacy Studies). 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 comorbidities]) . The most frequent ADR reported in immunocompromised children was vomiting (28%).

In a 12–week prophylaxis study in 475 immunocompromised 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 .

Laboratory Abnormalities

No text

2.6.2 Postmarketing Experience

The following adverse events have been identified during post-marketing use of Tamiflu. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency and/or establish a causal relationship to Tamiflu exposure.

Skin and subcutaneous tissue disorder: Hypersensitivity reactions such as allergic skin reactions including dermatitis, rash, eczema, urticaria, erythema multiforme, allergy, anaphylactic/anaphylactoid reactions, face oedema, Stevens-Johnson-Syndrome and toxic epidermal necrolysis have been reported.

Hepatobiliary disorder: hepatitis and elevated liver enzymes have been reported in patients with influenza-like illness receiving oseltamivir.

Psychiatric disorder/Nervous System Disorder: Convulsion and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares) have been reported during Tamiflu administration in patients with influenza, predominately in children and adolescents. In rare cases, these events resulted in accidental injury. The contribution of Tamiflu to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Tamiflu.

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

Laboratory Abnormalities

Elevated liver enzymes have been reported in patients with influenza-like illness receiving oseltamivir (see above under section 2.6.2 Postmarketing Experience)

2.7 OVERDOSE

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, described in section 2.6 Undesirable Effects.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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

In vitro studies demonstrated that neither oseltamivir phosphate nor the active metabolite is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases (see section 3.2 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 drugs has no effect on plasma levels of oseltamivir or its active metabolite.

Clinically important drug interactions involving competition for renal tubular secretion are unlikely due to the known safety margin for most of these drugs, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. Co-administration of probenecid results in approximate 2–fold increase in exposure to

the active metabolite due to a decrease in active tubular secretion in the kidney. However, due to the wide safety margin of the active metabolite, no dose adjustments are required when co-administering with probenecid.

Co-administration with amoxicillin does not alter plasma levels of either compound, indicating that competition for the anionic secretion pathway is weak . Co-administration with paracetamol does not alter plasma levels of oseltamivir, its active metabolite, or paracetamol. No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetyl-salicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), warfarin, rimantadine, or amantadine .

In phase III treatment and prophylaxis clinical studies, Tamiflu has been administered with commonly used drugs 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 agents (aspirin, ibuprofen and paracetamol). No change in adverse event profile or frequency has been observed as a result of co-administration of Tamiflu with these compounds.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action

Oseltamivir phosphate is a pro-drug of oseltamivir carboxylate (OC), a potent and selective inhibitor of influenza A and B virus neuraminidase enzymes. Viral neuraminidase is primarily important 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.

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

3.1.2 Clinical / Efficacy Studies

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

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

Trials in naturally occurring influenza

In phase III clinical trials conducted in the 1997–1998 Northern Hemisphere influenza season, patients were treated with Tamiflu for up to 40 hours after reported onset of symptoms. In these studies, 97% of patients were infected with influenza A and 3% with influenza B. Tamiflu treatment significantly reduced the duration of clinically relevant signs and symptoms of influenza by 32 hours. Disease severity in patients with confirmed influenza taking Tamiflu was also reduced by 38% compared to placebo. Moreover, Tamiflu reduced the incidence of complications associated

with influenza treated with antibiotic therapy in otherwise healthy young adults by approximately 50%. These complications include bronchitis, pneumonia, sinusitis and otitis media. In these phase III clinical trials there was clear evidence of efficacy in the secondary endpoints related to antiviral activity in terms of both reduction of duration of virus shedding and reduction in the AUC of viral titres.

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

Treatment of influenza in children

One double-blind placebo-controlled treatment trial was conducted in children, aged 1-12 (mean age 5.3), who had fever (> 100° F) plus one respiratory symptom (cough or coryza) when influenza virus was known to be circulating in the community. In this study 67% of influenza-infected patients were infected with influenza A and 33% with influenza B.

Tamiflu treatment, started within 48 hours of onset of symptoms, significantly reduced the duration of illness by 35.8 hours compared to placebo. Duration of illness was defined as time to alleviation of cough, nasal congestion, resolution of fever, and return to normal health and activity. The proportion of patients developing acute otitis media was reduced by 40% in children receiving Tamiflu vs placebo. Children receiving Tamiflu returned to normal health and activity almost 2 days earlier than those receiving placebo.

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

Treatment of influenza in immunocompromised patients (children, adolescents, and adults):

A randomized, double blind study, to evaluate safety and characterize the effects of oseltamivir on the development of resistant influenza virus (primary analysis) in influenza-infected immunocompromised patients, included 151 adult patients, 7 adolescents, and 9 children evaluable for efficacy of oseltamivir (secondary analysis, not powered).

The study included solid organ transplant [SOT] patients, haematopoietic stem cell transplant [HSCT] patients, HIV positive patients with a CD4+ cell count <500 cells/mm^3, patients on systemic immunosuppressive therapy, and those with haematological malignancy. These patients were randomized to be treated, within 96 hours of symptoms onset for a duration of 10 days. The treatment regimens were: standard dose 75 mg twice daily (73 adult patients, 4 adolescent patients, and 4 children) or double dose, 150 mg twice daily (78 adult patients, 3 adolescent patients, and 5 children) of oseltamivir, weight adjusted for children .

The median time to resolution of symptoms (TTRS) for adults and adolescents was similar between the standard dose group (103.4 hours [95% CI 75.4-122.7]) and double dose group

(107.2 hours [95% CI 63.90-140.0]). The TTRS for children was highly variable and the interpretation is limited by the small sample size.

The proportion of adult patients with secondary infections in the standard dose group and double dose group was comparable (8.2% vs 5.1%). For adolescents and children, only one patient (an adolescent) in the standard dose group experienced a secondary infection (bacterial sinusitis) .

The TTRS in all oseltamivir-treated adult immunocompromised patients (combined from both dose groups) was shorter when compared to matched placebo-treated otherwise healthy (reduced by 14 hours) and "at risk" patients (reduced by 60 hours), from previous studies.

A pharmacokinetics and pharmacodynamics study was conducted in severely immunocompromised children (≤12 years of age, n=30) receiving weight adjusted standard (75 mg twice daily) vs. triple dose (225 mg twice daily) of oseltamivir for an adaptive dosing period of 5-20 days (mean treatment duration: 9 days) . No patients in the standard dose group and 2 patients in the triple dose group reported secondary bacterial infections (bronchitis and sinusitis) .

The PK and PD data generated in the two studies supported the extrapolation of efficacy from immunocompromised adults to immunocompromised pediatric patients (<18 years old). (See Section 2.2 Dosage and Administration, Special Populations, 3.2.5 Pharmacokinetics for Special Populations).

Trials for prophylaxis of influenza

Prophylaxis of influenza in adults and adolescents

The efficacy of Tamiflu in preventing naturally occurring influenza A and B has been proven in three separate phase III studies.

In a phase III trial in adult and adolescent contacts of a household case of influenza, Tamiflu, started within 2 days of onset of symptoms in the household case and continued for seven days, significantly reduced the incidence of influenza illness occurring in the contacts by 92%.

In a double-blind placebo-controlled study conducted in unvaccinated otherwise healthy adults 18–65 years of age, Tamiflu significantly reduced the incidence of clinical influenza illness by 76% during a community outbreak of influenza. The subjects in this study received Tamiflu for a period of 42 days.

In a double-blind placebo-controlled study in elderly residents of nursing homes, 80% of whom had received vaccine in the season of the study, Tamiflu significantly reduced the incidence of clinical influenza illness by 92%. In the same study, Tamiflu significantly reduced the incidence of influenza associated bronchitis, pneumonia and sinusitis by 86%. The subjects in this study received Tamiflu for a period of 42 days.

In all three of the clinical trials, approximately 1% of subjects taking Tamiflu for prophylaxis developed influenza during the dosing period.

In these phase III clinical trials Tamiflu also significantly reduced the incidence of virus shedding and successfully prevented virus transmission in families.

Prophylaxis of influenza in Children

The efficacy of Tamiflu in preventing naturally occurring influenza illness has been demonstrated in a post exposure prophylaxis study in households that included children aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza. In this study, Tamiflu oral suspension 30 mg to 75 mg once daily taken for 10 days among children who were not already shedding virus at baseline reduced the incidence of laboratory-confirmed clinical influenza from 21% (15/70) in the group not receiving prophylaxis to 4% (2/47) in the group receiving prophylaxis.

Prophylaxis of influenza in Immunocompromised Patients

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

Viral resistance

Reduced sensitivity of viral neuraminidase

Treatment of Influenza

Clinical studies: The risk of emergence of influenza viruses with reduced susceptibility or resistance to oseltamivir has been examined during Roche-sponsored clinical studies. Patients who were found to carry oseltamivir-resistant virus generally did so transiently and showed no worsening of the underlying symptoms. In children a higher proportion of resistance was observed compared to adults and adolescents. In some pediatric patients, oseltamivir-resistant virus was detected for a prolonged period compared to patients carrying oseltamivir-sensitive virus; however, these patients showed 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 IC children, treated with Tamiflu across the two studies evaluated for resistance was 20.7% (6/29). Of the six IC children found with treatment-emergent resistance to oseltamivir, three 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.

Table 2 Incidence of Oseltamivir Resistance in Clinical Studies

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	**Geno- and Phenotyping***
Adults and adolescents	21/2382 (0.88%)	27/2396 (1.13%)
Children (1–12 years)	71/1726 (4.11%)	78/1727 (4.52%)
Infants <1 year	13/71 (18.31%)	13/71 (18.31%)

* 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 contacts (10 days) and seasonal (42 days) prevention of influenza in immunocompetent subjects. There was also no resistance observed during a 12–week prophylaxis study in immunocompromised subjects.

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.

Prescribers should consider available information on influenza virus drug susceptibility patterns for each season when deciding whether to use Tamiflu (for latest information, please refer to WHO and/or local government websites).

3.2 PHARMACOKINETIC PROPERTIES

3.2.1 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 section 2.2 Dosage and Administration).

3.2.2 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 drug interactions .

3.2.3 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 section 2.4.5 Interactions with other Medical Products and other Forms of Interaction).

3.2.4 Elimination

Absorbed oseltamivir is primarily (> 90%) eliminated by conversion to the active metabolite. The active metabolite is not further metabolized and is eliminated in the urine. Peak plasma concentrations of the active metabolite decline with a half-life of 6 to 10 hours in most subjects.

The active drug is eliminated entirely (> 99%) by renal excretion. Renal clearance (18.8 L/h) exceeds glomerular filtration rate (7.5 L/h) indicating that tubular secretion in addition to glomerular filtration occurs. Less than 20% of an oral radiolabelled dose is eliminated in faeces .

3.2.5 Pharmacokinetics in Special Populations

Pediatric Population

Children ≥ 1 year of age

The pharmacokinetics of Tamiflu have been evaluated in single dose pharmacokinetic studies in children aged 1 to 16 years. Multiple dose pharmacokinetics were studied in a small number of children aged 3–12 enrolled in a clinical trial. The rate of clearance of the active metabolite, corrected for bodyweight, was faster in younger children, than in adults, resulting in lower exposure in these children for a given mg/kg dose. Doses of 2 mg/kg and unit doses of 30 and 45 mg, administered to children in the appropriate categories according to the recommendation in section 2.2 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 Tamiflu have been evaluated in two open-label studies including influenza infected children less than one year of age (n=124). The rate of clearance of the active metabolite, corrected for body-weight, decreases with ages below one year. Metabolite exposures are also more variable in the youngest infants. The available data indicates that the exposure following a 3 mg/kg dose in 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 Tamiflu. Half-lives observed in the elderly were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for elderly patients for either the treatment or prophylaxis of influenza(see section 2.2.1 Special Dosage Instructions).

Renal impairment

Administration of 100 mg of Tamiflu twice daily for five days to patients with various degrees of renal impairment showed that exposure to the active metabolite is inversely proportional to declining renal function. For dosage information, see Section 2.2.1 Special Dosage Instructions.

Hepatic impairment

Based on in vitro and animal studies, significant increases in exposure to oseltamivir or its active metabolite are not expected and this has been confirmed in clinical studies in patients with mild or moderate hepatic impairment (see section 2.2.1 Special Dosage Instructions). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Pregnant Women

A pooled population pharmacokinetic analysis indicates that the Tamiflu dosage regimen described in Section 2.2 Dosage and Administration 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 (IC95 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.

Immunocompromised Patients

Population pharmacokinetic analyses indicate that treatment of adult and pediatric (<18 years old) immunocompromised patients with oseltamivir (as described in Section 2.2. Dosage and Administration) 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.

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 (see Section 3.1.2 Clinical/Efficacy Section).

3.3 NONCLINICAL SAFETY

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

3.3.1 Carcinogenicity

Three studies for carcinogenic potential (two-year rat and mouse studies with oseltamivir, and a six month transgenic Tg:AC mouse assay performed with the active metabolite) were negative.

3.3.2 Genotoxicity

Oseltamivir and the active metabolite were negative in the standard battery of genotoxicity assays.

3.3.3 Impairment of Fertility

A rat fertility study up to a dose of 1500 mg/kg/day demonstrated no adverse effects on either sex.

3.3.4 Reproductive Toxicity

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

3.3.5 Other

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

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

Whereas very high oral single doses of oseltamivir phosphate had no effect in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These effects were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse effects were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days, post-partum).

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Capsules:

As registered locally.

Do not store above 30°C: 48 months (4 years) shelf life.

or

Do not store above 25°C: up to 120 months (10 years) shelf life.

Powder for oral suspension:

As registered locally.

After reconstitution, the suspension can be stored at room temperature (not above 25°C) for 10 days or in a refrigerator (2°C–8°C) for 17 days.

Tamiflu should not be used after the expiry date (EXP) shown on the pack.

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

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

If the commercially manufactured Tamiflu oral suspension and the pharmacy compounded suspension are not available, Tamiflu suspension may be prepared from Tamiflu capsules at home (see Emergency Home Preparation of an Oral Suspension from Tamiflu Capsules).

For administering the pharmacy compounded suspension, syringes of appropriate volume and grading should be requested from the pharmacy. When the appropriate capsule strengths are not available for the dose needed, instructions for home preparation and syringes of appropriate volume and grading can be requested from the health care professional, such as a pharmacist).

Preparation of Tamiflu Powder for Oral Suspension (6 mg/mL)

It is recommended that Tamiflu powder for oral suspension be constituted by the pharmacist prior to dispensing to the patient (see section, 2.2 Dosage and Administration):

1. Tap the closed bottle 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 child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap.

The patient instruction sheet and an oral dispenser should be dispensed to the patient. It is recommended to write the date of expiration of the constituted suspension on the bottle label.

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: 25mL, 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	10 capsules	15 capsules	74 mL

	(450 mg)	(450 mg)	(450 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 room temperature “do not store above 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, drug 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 2.2 Dosage and Administration for the 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.

Dispense the suspension 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 appropriate 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 <30mg, 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 to Section 2.2 Dosage and Administration for the dosing instructions.

INCOMPATIBILITIES

Not applicable.

PACKS:

75 MG	10

DISPOSAL OF UNUSED/EXPIRED MEDICINES

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

Medicine: keep out of reach of children

Current at May 2021

Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel
Licenser:
Gilead Sciences, Foster City
California, USA

Any unused medicinal product or waste materials should be disposed of in accordance with local requirements.