ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 30 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains oseltamivir phosphate equivalent to 30 mg of oseltamivir.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule)
The hard capsule consists of a light yellow opaque body bearing the imprint “ROCHE” and a light yellow opaque cap bearing the imprint “30 mg”. Imprints are blue.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza
Tamiflu is indicated 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 two days of first onset of symptoms.

Prevention of influenza
- Post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

- The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.

- Tamiflu is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).

Tamiflu is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations (see section 5.1).

4.2 Posology and method of administration

Posology

Tamiflu hard capsules and Tamiflu suspension are bioequivalent formulations. 75 mg doses can be administered as either
- one 75 mg capsule or
- one 30 mg capsule plus one 45 mg capsule or

- by administering one 30 mg dose plus one 45 mg dose of suspension.

Commercially manufactured Tamiflu powder for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed.

Adults, and adolescents 13 years and over

Treatment: The recommended oral dose is 75 mg oseltamivir twice daily for 5 days for adolescents (13 to 17 years of age) and adults.

Body Weight	Recommended dose for 5 days
> 40 kg	75 mg twice daily

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days for adolescents (13 to 17 years of age) and adults.

Body Weight	Recommended dose for 10 days
> 40 kg	75 mg once daily

Therapy should begin as soon as possible within two days of exposure to an infected individual.

Prevention during an influenza epidemic in the community: The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to 6 weeks.

Paediatric population

Children 1 to 12 years of age

Tamiflu 30 mg, 45 mg and 75 mg capsules and oral suspension are available for infants and children 1 year of age or older

Treatment: The following weight-adjusted dosing regimens are recommended for treatment of infants and children 1 year of age or older:

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

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended post-exposure prevention dose of Tamiflu is:

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

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children below 12 years of age.

Infants 0 – 12 months of age

Treatment: The recommended treatment dose for infants 0 - 12 months of age is 3 mg/kg twice daily. This is based upon pharmacokinetic and safety data indicating that this dose in infants 0 - 12 months 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 5.2). The following dosing regimen is recommended for treatment of infants 0 - 12 months of age:

Body weight*	**Recommended dose for 5 days**
3 kg	9 mg twice daily
4 kg	12 mg twice daily
5 kg	15 mg twice daily
6 kg	18 mg twice daily
7 kg	21 mg twice daily
8 kg	24 mg twice daily
9 kg	27 mg twice daily
10 kg	30 mg twice daily

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

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Post-exposure prevention: The recommended prophylaxis dose for infants less than 1 year of age during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical data in infants and children 1 year of age or older and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza. The following age-adjusted dosing prophylaxis regimen is recommended for infants 0 - 12 months of age:

Age	**Recommended dose for 10 days**
0 - 12 months	3 mg/kg once daily

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This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children 0-12 months of age.

For instructions on preparing the extemporaneous formulation, see section 6.6.

Special populations

Hepatic impairment

No dose adjustment is required either for treatment or for prevention in patients with hepatic dysfunction. No studies have been carried out in paediatric patients with hepatic disorder.

Renal impairment
Treatment of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) twice daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) once daily
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) single dose

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

Prevention of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for prevention
> 60 (ml/min)	75 mg once daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) once daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) every second day
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after every second haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) once weekly

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

There is insufficient clinical data available in infants and children (12 years of age and younger) with renal impairment to be able to make any dosing recommendation.

Older people
No dose adjustment is required, unless there is evidence of moderate or severe renal impairment.

Immunocompromised patients
Longer duration of seasonal prophylaxis up to 12 weeks has been evaluated in immunocompromised patients (see sections 4.4, 4.8 and 5.1).

Method of administration
Oral use.
Patients who are unable to swallow capsules may receive appropriate doses of Tamiflu suspension.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses (see section 5.1).

Tamiflu is not a substitute for influenza vaccination. Use of Tamiflu must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as Tamiflu is administered. Tamiflu should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community. Susceptibility of circulating influenza virus strains to oseltamivir has been shown to be highly variable (see section 5.1). Therefore, prescribers should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use Tamiflu.

Severe concomitant condition
No information is available regarding the safety and efficacy of oseltamivir in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalisation.

Immunocompromised patients
The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established (see section 5.1).

Cardiac / respiratory disease
Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see section 5.1).

Paediatric population
No data allowing a dose recommendation for premature children (< 36 weeks post-conceptual age) are currently available.

Severe renal impairment
Dose adjustment is recommended for both treatment and prevention in adolescents (13 to 17 years of age) and adults with severe renal impairment. There is insufficient clinical data available in infants and children (1 year of age or older) with renal impairment to be able to make any dosing recommendation (see sections 4.2 and 5.2).

Neuropsychiatric events
Neuropsychiatric events have been reported during administration of Tamiflu in patients with influenza, especially in children and adolescents. These events are also experienced by patients with influenza without oseltamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see section 5.2), suggest that clinically significant drug interactions via these mechanisms are unlikely.

Probenecid
No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

Amoxicillin
Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that oseltamivir interaction with this pathway is weak.

Renal elimination
Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Additional information
No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetylsalicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), rimantadine or warfarin (in subjects stable on warfarin and without influenza).

4.6 Fertility, pregnancy and lactation

Pregnancy
While no controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, there is limited data available from post-marketing and retrospective observational surveillance reports. These data in conjunction with animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see section 5.3). Pregnant women may receive Tamiflu, after considering the available safety information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

Breastfeeding
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 subtherapeutic dose to the infant. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the breastfeeding woman, administration of oseltamivir may be considered, where there are clear potential benefits to breastfeeding mothers.

Fertility
Based on preclinical data, there is no evidence that Tamiflu has an effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Tamiflu is based on data from 6049 adult/adolescent and 1473 paediatric patients treated with Tamiflu or placebo for influenza, and on data from 3990 adult/adolescent and 253 paediatric patients receiving Tamiflu or placebo/no treatment for the prophylaxis of influenza in clinical trials. In addition, 475 immunocompromised patients (including 18 children, of these 10 Tamiflu and 8 placebo) received Tamiflu or placebo for the prophylaxis of influenza.

In adults/adolescents, the most commonly reported adverse reactions (ARs) were nausea and vomiting in the treatment studies, and nausea in the prevention studies. The majority of these ARs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. In children, the most commonly reported adverse reaction was vomiting. In the majority of patients, these ARs did not lead to discontinuation of Tamiflu.

The following serious adverse reactions have been rarely reported since oseltamivir has been marketed: Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders.
(Regarding neuropsychiatric disorders, see section 4.4.)

Tabulated list of adverse reactions
The ARs listed in the tables below fall into the following categories: 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*), and very rare (< *1/10,000*). ARs are added to the appropriate category in the tables according to the pooled analysis from clinical studies.

Treatment and prevention of influenza in adults and adolescents:
In adult/adolescent treatment and prevention studies, ARs that occurred the most frequently at the recommended dose (75 mg bid for 5 days for treatment and 75 mg od for up to 6 weeks for prophylaxis) are shown in Table 1.

The safety profile reported in subjects who 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, despite a longer duration of dosing in the prophylaxis studies.

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 arrhythmia	
Respiratory, thoracic and mediastinal disorders		Cough, Sore throat, Rhinorrhea		

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
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 prevention of influenza in children:

A total of 1473 children (including otherwise healthy children aged 1-12 years old and asthmatic children aged 6-12 years old) participated in clinical studies of oseltamivir given for the treatment of influenza. Of those, 851 children received treatment with oseltamivir suspension. A total of 158 children received the recommended dose of Tamiflu once daily in a post-exposure prophylaxis study in households (n = 99), a 6-week paediatric seasonal prophylaxis study (n = 49) and a 12-week paediatric seasonal prophylaxis study in immunocompromised subjects (n = 10).

Table 2 shows the most frequently reported ARs from paediatric clinical trials.

Table 2 Adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg o.d.])

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Otitis media,		
Nervous system disorders		Headache		
Eye disorders:		Conjunctivitis (including red eyes, eye discharge and eye pain)		
Ear and labyrinth disorders:		Earache	Tympanic membrane disorder	
Respiratory, thoracic and mediastinal disorders	Cough, Nasal congestion	Rhinorrhoea		
Gastrointestinal disorders	Vomiting	Abdominal pain (incl. upper abdominal pain), Dyspepsia, Nausea		
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)	

Description of selected adverse reactions

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

In patients with influenza who were receiving Tamiflu, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases resulting in self-injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. 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.

Hepato-biliary disorders
Hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.

Other special populations

Paediatric population (infants less than one year of age)
In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of oseltamivir therapy in 135 influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrohea and diaper rash being the most frequently reported

adverse events (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 oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies (comprising together more than 2,400 infants of that age class), epidemiological databases research and postmarketing reports suggest that the safety profile in infants less than one year of age is similar to the established safety profile of children aged one year and older.

Older people and patients with chronic cardiac and/or respiratory disease
The population included in the influenza treatment studies is comprised of otherwise healthy adults/adolescents and patients "at risk" (patients at higher risk of developing complications associated with influenza, e.g. older people 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.

Immunocompromised patients
In a 12-week prophylaxis study in 475 immunocompromised patients, including 18 children 1 to 12 years of age and older, the safety profile in the 238 patients who received oseltamivir was consistent with that previously observed in Tamiflu prophylaxis clinical studies.

Children with pre-existing bronchial asthma
In general, the adverse reaction profile in children with pre-existing bronchial asthma was qualitatively similar to that of otherwise healthy children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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 4.8 Undesirable effects.

No specific antidote is known.

Paediatric population
Overdose has been reported more frequently for children than adults and adolescents. Caution should be exercised when preparing Tamiflu oral suspension and when administering Tamiflu products to children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors ATC code: J05AH02

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into

uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published studies.

Clinical studies

Treatment of influenza infection

The indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A.

Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population, which included both influenza-positive and -negative subjects (ITT), primary efficacy was reduced proportionally to the number of influenza-negative individuals. In the overall treatment population, influenza infection was confirmed in 67 % (range 46 % to 74 %) of the recruited patients. Of the older subjects, 64 % were influenza-positive and of those with chronic cardiac and/or respiratory disease 62 % were influenza-positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents 13 years of age and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥ 37.8 °C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2,413) enrolled into treatment studies, oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95 % CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95 % CI 4.0 – 4.4 days; $p \leq 0.0001$).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1,063) in the placebo group to 8.6 % (116/1,350) in the oseltamivir treated population ($p = 0.0012$).

Treatment of influenza in high risk populations: The median duration of influenza illness in older subjects (≥ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In influenza-positive older people , oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics from 19 % (52/268) in the placebo group to 12 % (29/250) in the oseltamivir treated population ($p = 0.0156$).

In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17 % (22/133) in the placebo group and 14 % (16/118) in the oseltamivir treated population ($p = 0.5976$).

Treatment of influenza in children: In a study of otherwise healthy children (65 % influenza-positive) aged 1 to 12 years (mean age 5.3 years) who had fever (≥ 37.8 °C) plus either cough or coryza, 67 %

of influenza-positive patients were infected with influenza A and 33 % with influenza B. Oseltamivir treatment, started within 48 hours of onset of symptoms, significantly reduced the time to freedom from illness (defined as the simultaneous return to normal health and activity and alleviation of fever, cough and coryza) by 1.5 days (95 % CI 0.6 – 2.2 days; $p < 0.0001$) compared to placebo. Oseltamivir reduced the incidence of acute otitis media from 26.5 % (53/200) in the placebo group to 16 % (29/183) in the oseltamivir treated children ($p = 0.013$).

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) FEV_1 had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo ($p = 0.0148$) in this population.

The European Medicines Agency has deferred the obligation to submit the results of studies with Tamiflu in one or more subsets of the paediatric population in influenza. See section 4.2 for information on paediatric use.

The indication in infants below the age of 1 is based upon extrapolation of efficacy data from older children and the recommended posology is based upon pharmacokinetic modelling data (see Section 5.2).

Treatment of influenza B infection: Overall, 15 % of the influenza-positive population were infected by influenza B, proportions ranging from 1 to 33 % in individual studies. The median duration of illness in influenza B infected subjects did not differ significantly between the treatment groups in individual studies. Data from 504 influenza B infected subjects were pooled across all studies for analysis. Oseltamivir reduced the time to alleviation of all symptoms by 0.7 days (95 % CI 0.1 – 1.6 days; $p = 0.022$) and the duration of fever (≥ 37.8 °C), cough and coryza by one day (95 % CI 0.4 – 1.7 days; $p < 0.001$) compared to placebo.

Prevention of influenza
The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory-confirmed influenza. The virulence of influenza epidemics is not predictable and varies within a region and from season to season, therefore the number needed to treat (NNT) in order to prevent one case of influenza illness varies.

Post-exposure prevention: In a study in contacts (12.6 % vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily was started within 2 days of onset of symptoms in the index case and continued for seven days. Influenza was confirmed in 163 out of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12 %) in the placebo group to 2/205 (1 %) in the oseltamivir group (92 % reduction [95 % CI 6 – 16; $p \leq 0.0001$]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95 % CI 9 – 12) and was 16 (95 % CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and 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 the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20 % (27/136) in the group not receiving prevention to 7 % (10/135) in the group receiving prevention (62.7 % reduction [95 % CI 26.0 – 81.2; $p = 0.0042$]). In households of influenza-infected index cases, there was a reduction in the incidence of influenza from 26 % (23/89) in the group not receiving prevention to 11 % (9/84) in the group receiving prevention (58.5 % reduction [95 % CI 15.6 – 79.6; $p = 0.0114$]).
According to subgroup analysis in children at 1 to 12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21/111) in the

group not receiving prevention to 7 % (7/104) in the group receiving prevention (64.4 % reduction [95 % CI 15.8 – 85.0; p = 0.0188]). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15/70) in the group not receiving prevention to 4 % (2/47) in the group receiving prevention (80.1 % reduction [95 % CI 22.0 – 94.9; p = 0.0206]). The NNT for the total paediatric population was 9 (95 % CI 7 – 24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTII), respectively.

Prevention during an influenza epidemic in the community: In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25/519 (4.8 %) in the placebo group to 6/520 (1.2 %) in the oseltamivir group (76 % reduction [95 % CI 1.6 – 5.7; p = 0.0006]) during a community outbreak of influenza. The NNT in this study was 28 (95 % CI 24 – 50).
A study in older people in nursing homes, where 80 % of participants received vaccine in the season of the study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4 %) in the placebo group to 1/276 (0.4 %) in the oseltamivir group (92 % reduction [95 % CI 1.5 – 6.6; p = 0.0015]). The NNT in this study was 25 (95 % CI 23 – 62).

Prophylaxis of influenza in immunocompromised patients: A double-blind, placebo-controlled, randomised study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised patients (388 patients with solid organ transplantation [195 placebo; 193 oseltamivir], 87 patients with haemopoetic stem cell transplantation [43 placebo; 44 oseltamivir], no patient with other immunosuppressant conditions), including 18 children 1 to 12 years of age. The primary endpoint in this study was the incidence of laboratory-confirmed clinical influenza as determined by viral culture and/or a four-fold rise in HAI antibodies. The incidence of laboratory-confirmed clinical influenza was 2.9 % (7/238) in the placebo group and 2.1 % (5/237) in the oseltamivir group (95 % CI -2.3 % – 4.1 %; p = 0.772).

Specific studies have not been conducted to assess the reduction in the risk of complications.

Oseltamivir 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. All patients who were found to carry oseltamivir-resistant virus did so transiently, cleared the virus normally and showed no clinical deterioration.

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	**Geno- and Phenotyping***
Adults and adolescents	4/1,245 (0.32 %)	5/1,245 (0.4 %)
Children (1-12 years)	19/464 (4.1 %)	25/464 (5.4 %)

* Full genotyping was not performed in all studies.

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. Resistant strains selected during oseltamivir treatment have been isolated from both immunocompetent and immunocompromised patients. Immunocompromised patients and young children are at a higher risk of developing oseltamivir-resistant virus during treatment.

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. Since 2007 resistance

associated H275Y mutation in seasonal H1N1 strains has become widespread. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. In 2008, H275Y was found in > 99 % of circulating H1N1 influenza isolates in Europe. The 2009 H1N1 influenza ("swine flu") was almost uniformly susceptible to oseltamivir, with only sporadic reports of resistance in connection with both therapeutic and prophylactic regimens.

5.2 Pharmacokinetic properties

General Information

Absorption
Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5 % relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution
The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate distributes to all sites of influenza virus spread.

The binding of the oseltamivir carboxylate to human plasma protein is negligible (approximately 3 %).

Biotransformation
Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In vitro* studies demonstrated that neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination
Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds glomerular filtration rate (7.5 l/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Other special populations

Paediatric population

Infants less than 1 year of age: The pharmacokinetics, pharmacodynamics and safety of Tamiflu have been evaluated in two uncontrolled open-label studies including influenza infected children less than one year of age (n=135). 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 infants 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 (see sections 4.1 and 4.2).The reported adverse events were consistent with the established safety profile in older children.

There are no data available for infants below 1 year of age for post exposure prevention of influenza. Prevention during an influenza epidemic in the community has not been studied in children below 12 years of age.

Infants and children 1 year of age or older: The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in infants, children and adolescents 1 to 16 years of age. Multiple-dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the pro-drug and its active metabolite faster than adults, resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older are similar to those in adults.

Older people
Exposure to the active metabolite at steady state was 25 to 35 % higher in older people (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in older people were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for older people unless there is evidence of moderate or severe renal impairment (creatinine clearance below 60 ml /min) (see section 4.2).

Renal impairment
Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see section 4.2.

Hepatic impairment
In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of Tamiflu in its adopted therapeutic indications.

Teratology studies have been conducted in rats and rabbits at doses of up to 1,500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal development were observed. A rat fertility study up to a dose of 1,500 mg/kg/day demonstrated no adverse reactions on either sex. In pre- and post-natal rat studies, prolonged parturition was noted at 1,500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in 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 sensitisation to oseltamivir was observed in a "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active substance showed erythema after challenging the induced animals. Reversible irritancy of rabbits' eyes was detected.

Whereas very high oral single doses of oseltamivir phosphate salt, up to the highest dose tested (1,310 mg/kg), had no adverse reactions in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These reactions were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse reactions were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days post partum).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core
Pregelatinised starch (derived from maize starch)
Talc
Povidone
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Gelatin
Yellow iron oxide (E172)
Red iron oxide (E172)
Titanium dioxide (E171)

Printing ink
Shellac
Titanium dioxide (E171)
FD and C Blue 2 (indigo carmine, E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

7 years

Storage of the pharmacy compounded suspension
Shelf life of 10 days when stored below 25 °C.

6.4 Special precautions for storage

Do not store above 25 °C.

For storage conditions of the pharmacy compounded suspension, see section 6.3.

6.5 Nature and contents of container

Triplex blister pack (PVC/PE/PVDC, sealed with aluminium foil).
Pack-size 10 capsules.

6.6 Special precautions for disposal and other handling

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

Extemporaneous formulation

When Tamiflu powder for oral suspension is not available
Commercially manufactured Tamiflu for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. In the event that commercially manufactured Tamiflu powder for oral suspension is not

available, the pharmacist may compound a suspension (6 mg/ml) from Tamiflu capsules or patients can prepare the suspension from capsules at home.

The pharmacy preparation should be preferred to home preparation. Detailed information on the home preparation can be found in the package leaflet of Tamiflu capsules under “Making liquid Tamiflu at home”.

Syringes of appropriate volume and grading should be provided for administering the pharmacy compounded suspension as well as for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the syringes.

Pharmacy compounding

Pharmacy compounded 6 mg/ml suspension prepared from capsules

Adults, adolescents and infants and children 1 year of age or older who are unable to swallow intact capsules
This procedure describes the preparation of a 6 mg/ml suspension that will provide one patient with enough medicine for a 5-day course of treatment or a 10-day course of prophylaxis.

The pharmacist may compound a 6 mg/ml suspension 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 to provide a 5-day course of treatment or a 10-day course of prophylaxis for the patient. The total volume required is determined by the weight of the patient according to the recommendation in the table below. To allow for accurate volume withdrawal of up to 10 doses (2 withdrawals per daily treatment dose for 5 days), the column indicating measurement loss is to be considered for compounding.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient’s weight

Body weight (kg)	**Total volume to compound per patient weight (ml) Measurement loss not considered**	**Total volume to compound per patient weight (ml) Measurement loss considered**
10 kg to 15 kg	50 ml	60 ml or 75 ml*
> 15 kg to 23 kg	75 ml	90 ml or 100 ml*
> 23 kg to 40 kg	100 ml	125 ml
> 40 kg	125 ml	137.5 ml (or 150 ml)*

* Depending on the capsule strength used.
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) of pharmacy compounded 6 mg/ml suspension as shown in the table below:

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension

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	
60 ml	Please use alternative capsule strength*	8 capsules (360 mg)	12 capsules (360 mg)	59.5 ml
75 ml	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	74 ml
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
125 ml	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	123.5 ml
137.5 ml	11 capsules (825 mg)	Please use alternative capsule strength*	Please use alternative capsule strength*	136 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

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

1. In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
2. Open the stated amount of Tamiflu capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.
3. With a suitable stirring device, stir for 2 minutes.
   (Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Tamiflu capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Close the bottle using a child-resistant cap.
6. Put an ancillary label on the bottle indicating “Shake Gently Before Use”.
   (Note: This compounded suspension should be gently shaken prior to administration to minimise the tendency for air entrapment.)
7. Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date label according to storage condition (see section 6.3).

Place a pharmacy label on the bottle that includes the patient’s name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.

Dosing chart for pharmacy-compounded 6 mg/ml suspension prepared from Tamiflu capsules for infants and children 1 year of age or older

Body weight (kg)	Dose (mg)	Volume per dose 6 mg/ml	Treatment dose (for 5 days)	Prophylaxis dose (for 10 days)
10 kg to 15 kg	30 mg	5 ml	5 ml twice daily	5 ml once daily
> 15 kg to 23 kg	45 mg	7.5 ml	7.5 ml twice daily	7.5 ml once daily
> 23 kg to 40 kg	60 mg	10 ml	10 ml twice daily	10 ml once daily
> 40 kg	75 mg	12.5 ml	12.5 ml twice daily	12.5 ml once daily

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing table above) on the oral syringe for each patient.

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

Infants less than 1 year of age

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 or a 10-day course of prophylaxis.

The pharmacist may compound a 6 mg/ml suspension 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. To allow for accurate volume withdrawal of up to 10 doses (2 withdrawals per daily treatment dose for 5 days), the column indicating measurement loss is to be considered for compounding.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight

Body weight (kg)	Total volume to compound per patient weight (ml) Measurement loss not considered	Total volume to compound per patient weight (ml) Measurement loss considered
≤ 7 kg	up to 40 ml	50 ml
> 7 kg to 10 kg	50 ml	60 ml or 75 ml*

* Depending on the capsule strength used.

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) of pharmacy compounded 6 mg/ml suspension as shown in the table below:

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension

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	
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)	59.5 ml
75 ml	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	74 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

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

1. In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
2. Open the stated amount of Tamiflu capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.
3. With a suitable stirring device, stir for 2 minutes.
   (Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Tamiflu capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Close the bottle using a child-resistant cap.
6. Put an ancillary label on the bottle indicating “Shake Gently Before Use”.
   (Note: This compounded suspension should be gently shaken prior to administration to minimise the tendency for air entrapment.)
7. Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date label according to storage condition (see section 6.3).

Place a pharmacy label on the bottle that includes the patient’s name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.

Dosing chart for pharmacy compounded 6 mg/ml suspension prepared from Tamiflu capsules for infants less than 1 year of age

Body Weight (rounded to the nearest 0.5 kg)	Dose (mg)	Volume per dose (6 mg/ml)	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)	Dispenser size to use (grading 0.1 ml)
3 kg	9 mg	1.5 ml	1.5 ml twice daily	1.5 ml once daily	2.0 ml or 3.0 ml
3.5 kg	10.5 mg	1.8 ml	1.8 ml twice daily	1.8 ml once daily	2.0 ml or 3.0 ml
4 kg	12 mg	2.0 ml	2.0 ml twice daily	2.0 ml once daily	3.0 ml
4.5 kg	13.5 mg	2.3 ml	2.3 ml twice daily	2.3 ml once daily	3.0 ml
5 kg	15 mg	2.5 ml	2.5 ml twice daily	2.5 ml once daily	3.0 ml
5.5 kg	16.5 mg	2.8 ml	2.8 ml twice daily	2.8 ml once daily	3.0 ml
6 kg	18 mg	3.0 ml	3.0 ml twice daily	3.0 ml once daily	3.0 ml (or 5.0 ml)
6.5 kg	19.5 mg	3.3 ml	3.3 ml twice daily	3.3 ml once daily	5.0 ml
7 kg	21 mg	3.5 ml	3.5ml twice daily	3.5 ml once daily	5.0 ml
7.5 kg	22.5 mg	3.8 ml	3.8 ml twice daily	3.8 ml once daily	5.0 ml
8 kg	24 mg	4.0 ml	4.0 ml twice daily	4.0 ml once daily	5.0 ml
8.5 kg	25.5 mg	4.3 ml	4.3 ml twice daily	4.3 ml once daily	5.0 ml
9 kg	27 mg	4.5 ml	4.5 ml twice daily	4.5 ml once daily	5.0 ml
9.5 kg	28.5 mg	4.8 ml	4.8 ml twice daily	4.8 ml once daily	5.0 ml
10 kg	30 mg	5.0 ml	5.0 ml twice daily	5.0 ml once daily	5.0 ml

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing tables above) on the oral syringe for each patient.

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

Home preparation

When commercially manufactured Tamiflu oral suspension is not available, a pharmacy compounded suspension prepared from Tamiflu capsules must be used (see detailed instructions above). If the commercially manufactured Tamiflu oral suspension and the pharmacy compounded suspension is also not available, Tamiflu suspension may be prepared at home.

When appropriate capsule strengths are available for the dose needed, the dose is given by opening the capsule and mixing its contents with no more than one teaspoon of a suitable sweetened food product. The bitter taste can be masked by products such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce). 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, the preparation of Tamiflu suspension involves additional steps. Detailed instructions can be found in the package leaflet of Tamiflu capsules under “Making liquid Tamiflu at home”.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2002
Date of last renewal: 20 June 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 45 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains oseltamivir phosphate equivalent to 45 mg of oseltamivir.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza
Tamiflu is indicated 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 two days of first onset of symptoms.

Prevention of influenza
- Post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

- The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.

- Tamiflu is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).

Tamiflu is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations (see section 5.1).

4.2 Posology and method of administration

Posology

Tamiflu hard capsules and Tamiflu suspension are bioequivalent formulations. 75 mg doses can be administered as either
- one 75 mg capsule or
- one 30 mg capsule plus one 45 mg capsule or
- by administering one 30 mg dose plus one 45 mg dose of suspension.

Commercially manufactured Tamiflu powder for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed.

Adults, and adolescents 13 years and over

Treatment: The recommended oral dose is 75 mg oseltamivir twice daily for 5 days for adolescents (13 to 17 years of age) and adults.

Body Weight	Recommended dose for 5 days
> 40 kg	75 mg twice daily

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days for adolescents (13 to 17 years of age) and adults.

Body Weight	Recommended dose for 10 days
> 40 kg	75 mg once daily

Therapy should begin as soon as possible within two days of exposure to an infected individual.

Prevention during an influenza epidemic in the community: The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to 6 weeks.

Paediatric population

Children 1 to 12 years of age

Tamiflu 30 mg, 45 mg and 75 mg capsules and oral suspension are available for infants and children 1 year of age or older

Treatment: The following weight-adjusted dosing regimens are recommended for treatment of infants and children 1 year of age or older:

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

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended post-exposure prevention dose of Tamiflu is:

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

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children below 12 years of age.

For infants 0 - 12 months of age

Treatment: The recommended treatment dose for infants 0 - 12 months of age is 3 mg/kg twice daily. This is based upon pharmacokinetic and safety data indicating that this dose in infants 0 - 12 months 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 5.2). The following dosing regimen is recommended for treatment of infants 0 - 12 months of age:

Body weight*	**Recommended dose for 5 days**
3 kg	9 mg twice daily
4 kg	12 mg twice daily
5 kg	15 mg twice daily
6 kg	18 mg twice daily
7 kg	21 mg twice daily
8 kg	24 mg twice daily
9 kg	27 mg twice daily
10 kg	30 mg 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.

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Post-exposure prevention: The recommended prophylaxis dose for infants less than 1 year of age during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical data in infants and children 1 year of age or older and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza. The following age-adjusted dosing prophylaxis regimen is recommended for infants 0 - 12 months of age:

Age	**Recommended dose for 10 days**
0 - 12 months	3 mg/kg once daily

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children 0-12 months of age.

For instructions on preparing the extemporaneous formulation, see section 6.6.

Special populations

Hepatic impairment

No dose adjustment is required either for treatment or for prevention in patients with hepatic dysfunction. No studies have been carried out in paediatric patients with hepatic disorder.

Renal impairment
Treatment of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) twice daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) once daily
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) single dose

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

Prevention of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for prevention
> 60 (ml/min)	75 mg once daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) once daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) every second day
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after every second haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) once weekly

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

There is insufficient clinical data available in infants and children (12 years of age and younger) with renal impairment to be able to make any dosing recommendation.

Older people
No dose adjustment is required, unless there is evidence of moderate or severe renal impairment.

Immunocompromised patients
Longer duration of seasonal prophylaxis up to 12 weeks has been evaluated in immunocompromised patients (see sections 4.4, 4.8 and 5.1).

Method of administration
Oral use.
Patients who are unable to swallow capsules may receive appropriate doses of Tamiflu suspension.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses (see section 5.1).

Tamiflu is not a substitute for influenza vaccination. Use of Tamiflu must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as

Tamiflu is administered. Tamiflu should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community. Susceptibility of circulating influenza virus strains to oseltamivir has been shown to be highly variable (see section 5.1). Therefore, prescribers should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use Tamiflu.

Severe concomitant condition
No information is available regarding the safety and efficacy of oseltamivir in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalisation.

Immunocompromised patients
The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established (see section 5.1).

Cardiac / respiratory disease
Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see section 5.1).

Paediatric population
No data allowing a dose recommendation for premature children (<36 weeks post-conceptual age) are currently available.

Severe renal impairment
Dose adjustment is recommended for both treatment and prevention in adolescents (13 to 17 years of age) and adults with severe renal impairment. There is insufficient clinical data available in infants and children (1 year of age or older) with renal impairment to be able to make any dosing recommendation (see sections 4.2 and 5.2).

Neuropsychiatric events
Neuropsychiatric events have been reported during administration of Tamiflu in patients with influenza, especially in children and adolescents. These events are also experienced by patients with influenza without oseltamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see section 5.2), suggest that clinically significant drug interactions via these mechanisms are unlikely.

Probenecid
No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

Amoxicillin
Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that oseltamivir interaction with this pathway is weak.

Renal elimination
Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of

these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Additional information
No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetylsalicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), rimantadine or warfarin (in subjects stable on warfarin and without influenza).

4.6 Fertility, pregnancy and lactation

Pregnancy
While no controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, there is limited data available from post-marketing and retrospective observational surveillance reports. These data in conjunction with animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see section 5.3). Pregnant women may receive Tamiflu, after considering the available safety information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

Breastfeeding
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 subtherapeutic dose to the infant. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the breastfeeding woman, administration of oseltamivir may be considered, where there are clear potential benefits to breastfeeding mothers.

Fertility
Based on preclinical data, there is no evidence that Tamiflu has an effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Tamiflu is based on data from 6049 adult/adolescent and 1473 paediatric patients treated with Tamiflu or placebo for influenza, and on data from 3990 adult/adolescent and 253 paediatric patients receiving Tamiflu or placebo/no treatment for the prophylaxis of influenza in clinical trials. In addition, 475 immunocompromised patients (including 18 children, of these 10 Tamiflu and 8 placebo) received Tamiflu or placebo for the prophylaxis of influenza.

In adults/adolescents, the most commonly reported adverse reactions (ARs) were nausea and vomiting in the treatment studies, and nausea in the prevention studies. The majority of these ARs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. In children, the most commonly reported adverse reaction was vomiting. In the majority of patients, these ARs did not lead to discontinuation of Tamiflu.

The following serious adverse reactions have been rarely reported since oseltamivir has been marketed: Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders.
(Regarding neuropsychiatric disorders, see section 4.4.)

Tabulated list of adverse reactions

The ARs listed in the tables below fall into the following categories: 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*), and very rare (< *1/10,000*). ARs are added to the appropriate category in the tables according to the pooled analysis from clinical studies.

Treatment and prevention of influenza in adults and adolescents:

In adult/adolescent treatment and prevention studies, ARs that occurred the most frequently at the recommended dose (75 mg bid for 5 days for treatment and 75 mg od for up to 6 weeks for prophylaxis) are shown in Table 1.

The safety profile reported in subjects who 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, despite a longer duration of dosing in the prophylaxis studies.

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 arrhythmia	
Respiratory, thoracic and mediastinal disorders		Cough, Sore throat, Rhinorrhea		

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
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 prevention of influenza in children:

A total of 1473 children (including otherwise healthy children aged 1-12 years old and asthmatic children aged 6-12 years old) participated in clinical studies of oseltamivir given for the treatment of influenza. Of those, 851 children received treatment with oseltamivir suspension. A total of 158 children received the recommended dose of Tamiflu once daily in a post-exposure prophylaxis study in households (n = 99), a 6-week paediatric seasonal prophylaxis study (n = 49) and a 12-week paediatric seasonal prophylaxis study in immunocompromised subjects (n = 10).

Table 2 shows the most frequently reported ARs from paediatric clinical trials.

Table 2 Adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg o.d.])

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Otitis media,		
Nervous system disorders		Headache		
Eye disorders:		Conjunctivitis (including red eyes, eye discharge and eye pain)		
Ear and labyrinth disorders:		Earache	Tympanic membrane disorder	
Respiratory, thoracic and mediastinal disorders	Cough, Nasal congestion	Rhinorrhoea		
Gastrointestinal disorders	Vomiting	Abdominal pain (incl. upper abdominal pain), Dyspepsia, Nausea		
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)	

Description of selected adverse reactions

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

In patients with influenza who were receiving Tamiflu, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases resulting in self-injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. 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.

Hepato-biliary disorders
Hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.

Other special populations

Paediatric population (infants less than one year of age)
In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of oseltamivir therapy in 135 influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrohea and diaper rash being the most frequently reported

adverse events (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 oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies (comprising together more than 2,400 infants of that age class), epidemiological databases research and postmarketing reports suggest that the safety profile in infants less than one year of age is similar to the established safety profile of children aged one year and older.

Older people and patients with chronic cardiac and/or respiratory disease
The population included in the influenza treatment studies is comprised of otherwise healthy adults/adolescents and patients “at risk” (patients at higher risk of developing complications associated with influenza, e.g. older people 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.

Immunocompromised patients
In a 12-week prophylaxis study in 475 immunocompromised patients, including 18 children 1 to 12 years of age and older, the safety profile in the 238 patients who received oseltamivir was consistent with that previously observed in Tamiflu prophylaxis clinical studies.

Children with pre-existing bronchial asthma
In general, the adverse reaction profile in children with pre-existing bronchial asthma was qualitatively similar to that of otherwise healthy children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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 4.8 Undesirable effects.

No specific antidote is known.

Paediatric population
Overdose has been reported more frequently for children than adults and adolescents. Caution should be exercised when preparing Tamiflu oral suspension and when administering Tamiflu products to children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors ATC code: J05AH02

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into

uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published studies.

Clinical studies

Treatment of influenza infection

The indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A.

Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population, which included both influenza-positive and -negative subjects (ITT), primary efficacy was reduced proportionally to the number of influenza-negative individuals. In the overall treatment population, influenza infection was confirmed in 67 % (range 46 % to 74 %) of the recruited patients. Of the older subjects, 64 % were influenza-positive and of those with chronic cardiac and/or respiratory disease 62 % were influenza-positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents 13 years of age and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥ 37.8 °C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2,413) enrolled into treatment studies, oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95 % CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95 % CI 4.0 – 4.4 days; $p \leq 0.0001$).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1,063) in the placebo group to 8.6 % (116/1,350) in the oseltamivir treated population ($p = 0.0012$).

Treatment of influenza in high risk populations: The median duration of influenza illness in older subjects (≥ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In influenza-positive older people, oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics from 19 % (52/268) in the placebo group to 12 % (29/250) in the oseltamivir treated population ($p = 0.0156$).

In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17 % (22/133) in the placebo group and 14 % (16/118) in the oseltamivir treated population ($p = 0.5976$).

Treatment of influenza in children: In a study of otherwise healthy children (65 % influenza-positive) aged 1 to 12 years (mean age 5.3 years) who had fever (≥ 37.8 °C) plus either cough or coryza, 67 % of influenza-positive patients were infected with influenza A and 33 % with influenza B. Oseltamivir treatment, started within 48 hours of onset of symptoms, significantly reduced the time to freedom from illness (defined as the simultaneous return to normal health and activity and alleviation of fever,

cough and coryza) by 1.5 days (95 % CI 0.6 – 2.2 days; $p < 0.0001$) compared to placebo. Oseltamivir reduced the incidence of acute otitis media from 26.5 % (53/200) in the placebo group to 16 % (29/183) in the oseltamivir treated children ($p = 0.013$).

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) FEV_1 had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo ($p = 0.0148$) in this population.

The European Medicines Agency has deferred the obligation to submit the results of studies with Tamiflu in one or more subsets of the paediatric population in influenza. See section 4.2 for information on paediatric use.

The indication in infants below the age of 1 is based upon extrapolation of efficacy data from older children and the recommended posology is based upon pharmacokinetic modelling data (see Section 5.2).

Treatment of influenza B infection: Overall, 15 % of the influenza-positive population were infected by influenza B, proportions ranging from 1 to 33 % in individual studies. The median duration of illness in influenza B infected subjects did not differ significantly between the treatment groups in individual studies. Data from 504 influenza B infected subjects were pooled across all studies for analysis. Oseltamivir reduced the time to alleviation of all symptoms by 0.7 days (95 % CI 0.1 – 1.6 days; $p = 0.022$) and the duration of fever (≥ 37.8 °C), cough and coryza by one day (95 % CI 0.4 – 1.7 days; $p < 0.001$) compared to placebo.

Prevention of influenza
The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory-confirmed influenza. The virulence of influenza epidemics is not predictable and varies within a region and from season to season, therefore the number needed to treat (NNT) in order to prevent one case of influenza illness varies.

Post-exposure prevention: In a study in contacts (12.6 % vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily was started within 2 days of onset of symptoms in the index case and continued for seven days. Influenza was confirmed in 163 out of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12 %) in the placebo group to 2/205 (1 %) in the oseltamivir group (92 % reduction [95 % CI 6 – 16; $p \leq 0.0001$]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95 % CI 9 – 12) and was 16 (95 % CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and 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 the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20 % (27/136) in the group not receiving prevention to 7 % (10/135) in the group receiving prevention (62.7 % reduction [95 % CI 26.0 – 81.2; $p = 0.0042$]). In households of influenza-infected index cases, there was a reduction in the incidence of influenza from 26 % (23/89) in the group not receiving prevention to 11 % (9/84) in the group receiving prevention (58.5 % reduction [95 % CI 15.6 – 79.6; $p = 0.0114$]).
According to subgroup analysis in children at 1 to 12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21/111) in the group not receiving prevention to 7 % (7/104) in the group receiving prevention (64.4 % reduction [95 % CI 15.8 – 85.0; $p = 0.0188$]). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15/70) in the group

not receiving prevention to 4 % (2/47) in the group receiving prevention (80.1 % reduction [95 % CI 22.0 – 94.9; p = 0.0206]). The NNT for the total paediatric population was 9 (95 % CI 7 – 24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTII), respectively.

Prevention during an influenza epidemic in the community: In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25/519 (4.8 %) in the placebo group to 6/520 (1.2 %) in the oseltamivir group (76 % reduction [95 % CI 1.6 – 5.7; p = 0.0006]) during a community outbreak of influenza. The NNT in this study was 28 (95 % CI 24 – 50).
A study in older people in nursing homes, where 80 % of participants received vaccine in the season of the study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4 %) in the placebo group to 1/276 (0.4 %) in the oseltamivir group (92 % reduction [95 % CI 1.5 – 6.6; p = 0.0015]). The NNT in this study was 25 (95 % CI 23 – 62).

Prophylaxis of influenza in immunocompromised patients: A double-blind, placebo-controlled, randomised study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised patients (388 patients with solid organ transplantation [195 placebo; 193 oseltamivir], 87 patients with haemopoetic stem cell transplantation [43 placebo; 44 oseltamivir], no patient with other immunosuppressant conditions), including 18 children 1 to 12 years of age. The primary endpoint in this study was the incidence of laboratory-confirmed clinical influenza as determined by viral culture and/or a four-fold rise in HAI antibodies. The incidence of laboratory-confirmed clinical influenza was 2.9 % (7/238) in the placebo group and 2.1 % (5/237) in the oseltamivir group (95 % CI -2.3 % – 4.1 %; p = 0.772).

Specific studies have not been conducted to assess the reduction in the risk of complications.

Oseltamivir 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. All patients who were found to carry oseltamivir-resistant virus did so transiently, cleared the virus normally and showed no clinical deterioration.

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	Geno- and Phenotyping*
Adults and adolescents	4/1,245 (0.32 %)	5/1,245 (0.4 %)
Children (1-12 years)	19/464 (4.1 %)	25/464 (5.4 %)

* Full genotyping was not performed in all studies.

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. Resistant strains selected during oseltamivir treatment have been isolated from both immunocompetent and immunocompromised patients. Immunocompromised patients and young children are at a higher risk of developing oseltamivir-resistant virus during treatment.

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. Since 2007 resistance associated H275Y mutation in seasonal H1N1 strains has become widespread. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. In 2008, H275Y was found in > 99 % of circulating H1N1 influenza isolates in Europe. The 2009 H1N1

influenza (“swine flu”) was almost uniformly susceptible to oseltamivir, with only sporadic reports of resistance in connection with both therapeutic and prophylactic regimens.

5.2 Pharmacokinetic properties

General Information

Absorption
Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5 % relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution
The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate distributes to all sites of influenza virus spread.

The binding of the oseltamivir carboxylate to human plasma protein is negligible (approximately 3 %).

Biotransformation
Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In vitro* studies demonstrated that neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination
Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds glomerular filtration rate (7.5 l/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Other special populations

Paediatric population
Infants less than 1 year of age: The pharmacokinetics, pharmacodynamics and safety of Tamiflu have been evaluated in two uncontrolled open-label studies including influenza infected children less than one year of age (n=135). 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 infants 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 (see sections 4.1 and 4.2).The reported adverse events were consistent with the established safety profile in older children.

There are no data available for infants below 1 year of age for post exposure prevention of influenza. Prevention during an influenza epidemic in the community has not been studied in children below 12 years of age.

Infants and children 1 year of age or older: The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in infants, children and adolescents 1 to 16 years of age. Multiple-dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the pro-drug and its active metabolite faster than adults,

resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older are similar to those in adults.

Older people
Exposure to the active metabolite at steady state was 25 to 35 % higher in older people (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in older people were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for older people unless there is evidence of moderate or severe renal impairment (creatinine clearance below 60 ml /min) (see section 4.2).

Renal impairment
Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see section 4.2.

Hepatic impairment
In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of Tamiflu in its adopted therapeutic indications.

Teratology studies have been conducted in rats and rabbits at doses of up to 1,500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal development were observed. A rat fertility study up to a dose of 1,500 mg/kg/day demonstrated no adverse reactions on either sex. In pre- and post-natal rat studies, prolonged parturition was noted at 1,500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in 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 sensitisation to oseltamivir was observed in a "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active substance showed erythema after challenging the induced animals. Reversible irritancy of rabbits' eyes was detected.

Whereas very high oral single doses of oseltamivir phosphate salt, up to the highest dose tested (1,310 mg/kg), had no adverse reactions in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These reactions were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse reactions were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days post partum).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core
Pregelatinised starch (derived from maize starch)
Talc
Povidone
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Gelatin
Black iron oxide (E172)
Titanium dioxide (E171)

Printing ink
Shellac
Titanium dioxide (E171)
FD and C Blue 2 (indigo carmine, E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

7 years

Storage of the pharmacy compounded suspension
Shelf life of 10 days when stored below 25 °C.

6.4 Special precautions for storage

Do not store above 25 °C.

For storage conditions of the pharmacy compounded suspension, see section 6.3.

6.5 Nature and contents of container

Triplex blister pack (PVC/PE/PVDC, sealed with aluminium foil).
Pack-size 10 capsules.

6.6 Special precautions for disposal and other handling

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

Extemporaneous formulation

When Tamiflu powder for oral suspension is not available
Commercially manufactured Tamiflu for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. In the event that commercially manufactured Tamiflu powder for oral suspension is not available, the pharmacist may compound a suspension (6 mg/ml) from Tamiflu capsules or patients can prepare the suspension from capsules at home.

The pharmacy preparation should be preferred to home preparation. Detailed information on the home preparation can be found in the package leaflet of Tamiflu capsules under “Making liquid Tamiflu at home”.

Syringes of appropriate volume and grading should be provided for administering the pharmacy compounded suspension as well as for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the syringes.

Pharmacy compounding

Pharmacy compounded 6 mg/ml suspension prepared from capsules

Adults, adolescents and infants and children 1 year of age or older who are unable to swallow intact capsules
This procedure describes the preparation of a 6 mg/ml suspension that will provide one patient with enough medicine for a 5-day course of treatment or a 10-day course of prophylaxis.

The pharmacist may compound a 6 mg/ml suspension 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 to provide a 5-day course of treatment or a 10-day course of prophylaxis for the patient. The total volume required is determined by the weight of the patient according to the recommendation in the table below. To allow for accurate volume withdrawal of up to 10 doses (2 withdrawals per daily treatment dose for 5 days), the column indicating measurement loss is to be considered for compounding.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient’s weight

Body weight (kg)	**Total volume to compound per patient weight (ml) Measurement loss not considered**	**Total volume to compound per patient weight (ml) Measurement loss considered**
10 kg to 15 kg	50 ml	60 ml or 75 ml*
> 15 kg to 23 kg	75 ml	90 ml or 100 ml*
> 23 kg to 40 kg	100 ml	125 ml
> 40 kg	125 ml	137.5 ml (or 150 ml)*

* Depending on the capsule strength used.

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) of pharmacy compounded 6 mg/ml suspension as shown in the table below:

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension

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	
60 ml	Please use alternative capsule strength*	8 capsules (360 mg)	12 capsules (360 mg)	59.5 ml
75 ml	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	74 ml
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
125 ml	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	123.5 ml
137.5 ml	11 capsules (825 mg)	Please use alternative capsule strength*	Please use alternative capsule strength*	136 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

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

1. In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
2. Open the stated amount of Tamiflu capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.
3. With a suitable stirring device, stir for 2 minutes.
   (Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Tamiflu capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Close the bottle using a child-resistant cap.
6. Put an ancillary label on the bottle indicating “Shake Gently Before Use”.
   (Note: This compounded suspension should be gently shaken prior to administration to minimise the tendency for air entrapment.)
7. Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date label according to storage condition (see section 6.3).

Place a pharmacy label on the bottle that includes the patient’s name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.

Dosing chart for pharmacy-compounded 6 mg/ml suspension prepared from Tamiflu capsules for infants and children 1 year of age or older

Body weight (kg)	Dose (mg)	Volume per dose 6 mg/ml	Treatment dose (for 5 days)	Prophylaxis dose (for 10 days)
10 kg to 15 kg	30 mg	5 ml	5 ml twice daily	5 ml once daily
> 15 kg to 23 kg	45 mg	7.5 ml	7.5 ml twice daily	7.5 ml once daily
> 23 kg to 40 kg	60 mg	10 ml	10 ml twice daily	10 ml once daily
> 40 kg	75 mg	12.5 ml	12.5 ml twice daily	12.5 ml once daily

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing table above) on the oral syringe for each patient.

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

Infants less than 1 year of age

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 or a 10-day course of prophylaxis.

The pharmacist may compound a 6 mg/ml suspension 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. To allow for accurate volume withdrawal of up to 10 doses (2 withdrawals per daily treatment dose for 5 days), the column indicating measurement loss is to be considered for compounding.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight

Body weight (kg)	Total volume to compound per patient weight (ml) Measurement loss not considered	Total volume to compound per patient weight (ml) Measurement loss considered
≤ 7 kg	up to 40 ml	50 ml
> 7 kg to 10 kg	50 ml	60 ml or 75 ml*

* Depending on the capsule strength used.

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) of pharmacy compounded 6 mg/ml suspension as shown in the table below:

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension

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	
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)	59.5 ml
75 ml	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	74 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

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

1. In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
2. Open the stated amount of Tamiflu capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.
3. With a suitable stirring device, stir for 2 minutes.
   (Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Tamiflu capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Close the bottle using a child-resistant cap.
6. Put an ancillary label on the bottle indicating “Shake Gently Before Use”.
   (Note: This compounded suspension should be gently shaken prior to administration to minimise the tendency for air entrapment.)
7. Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date label according to storage condition (see section 6.3).

Place a pharmacy label on the bottle that includes the patient’s name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.

Dosing chart for pharmacy compounded 6 mg/ml suspension prepared from Tamiflu capsules for infants less than 1 year of age

Body Weight (rounded to the nearest 0.5 kg)	Dose (mg)	Volume per dose (6 mg/ml)	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)	Dispenser size to use (grading 0.1 ml)
3 kg	9 mg	1.5 ml	1.5 ml twice daily	1.5 ml once daily	2.0 ml or 3.0 ml
3.5 kg	10.5 mg	1.8 ml	1.8 ml twice daily	1.8 ml once daily	2.0 ml or 3.0 ml
4 kg	12 mg	2.0 ml	2.0 ml twice daily	2.0 ml once daily	3.0 ml
4.5 kg	13.5 mg	2.3 ml	2.3 ml twice daily	2.3 ml once daily	3.0 ml
5 kg	15 mg	2.5 ml	2.5 ml twice daily	2.5 ml once daily	3.0 ml
5.5 kg	16.5 mg	2.8 ml	2.8 ml twice daily	2.8 ml once daily	3.0 ml
6 kg	18 mg	3.0 ml	3.0 ml twice daily	3.0 ml once daily	3.0 ml (or 5.0 ml)
6.5 kg	19.5 mg	3.3 ml	3.3 ml twice daily	3.3 ml once daily	5.0 ml
7 kg	21 mg	3.5 ml	3.5ml twice daily	3.5 ml once daily	5.0 ml
7.5 kg	22.5 mg	3.8 ml	3.8 ml twice daily	3.8 ml once daily	5.0 ml
8 kg	24 mg	4.0 ml	4.0 ml twice daily	4.0 ml once daily	5.0 ml
8.5 kg	25.5 mg	4.3 ml	4.3 ml twice daily	4.3 ml once daily	5.0 ml
9 kg	27 mg	4.5 ml	4.5 ml twice daily	4.5 ml once daily	5.0 ml
9.5 kg	28.5 mg	4.8 ml	4.8 ml twice daily	4.8 ml once daily	5.0 ml
10 kg	30 mg	5.0 ml	5.0 ml twice daily	5.0 ml once daily	5.0 ml

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing tables above) on the oral syringe for each patient.

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

Home preparation

When commercially manufactured Tamiflu oral suspension is not available, a pharmacy compounded suspension prepared from Tamiflu capsules must be used (see detailed instructions above). If the commercially manufactured Tamiflu oral suspension and the pharmacy compounded suspension is also not available, Tamiflu suspension may be prepared at home.

When appropriate capsule strengths are available for the dose needed, the dose is given by opening the capsule and mixing its contents with no more than one teaspoon of a suitable sweetened food product. The bitter taste can be masked by products such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce). 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, the preparation of Tamiflu suspension involves additional steps. Detailed instructions can be found in the package leaflet of Tamiflu capsules under “Making liquid Tamiflu at home”.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2002
Date of last renewal: 20 June 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 75 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains oseltamivir phosphate equivalent to 75 mg of oseltamivir.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza
Tamiflu is indicated 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 two days of first onset of symptoms.

Prevention of influenza
- Post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

- The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.

- Tamiflu is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).

Tamiflu is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations (see section 5.1).

4.2 Posology and method of administration

Posology

Tamiflu hard capsules and Tamiflu suspension are bioequivalent formulations. 75 mg doses can be administered as either
- one 75 mg capsule or
- one 30 mg capsule plus one 45 mg capsule or
- by administering one 30 mg dose plus one 45 mg dose of suspension.

Commercially manufactured Tamiflu powder for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed.

Adults, and adolescents 13 years and over

Treatment: The recommended oral dose is 75 mg oseltamivir twice daily for 5 days for adolescents (13 to 17 years of age) and adults.

Body Weight	Recommended dose for 5 days
> 40 kg	75 mg twice daily

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days for adolescents (13 to 17 years of age) and adults.

Body Weight	Recommended dose for 10 days
> 40 kg	75 mg once daily

Therapy should begin as soon as possible within two days of exposure to an infected individual.

Prevention during an influenza epidemic in the community: The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to 6 weeks.

Paediatric population

Children 1 to 12 years of age

Tamiflu 30 mg, 45 mg and 75 mg capsules and oral suspension are available for infants and children 1 year of age or older

Treatment: The following weight-adjusted dosing regimens are recommended for treatment of infants and children 1 year of age or older:

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

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Post-exposure prevention: The recommended post-exposure prevention dose of Tamiflu is:

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

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children below 12 years of age.

For infants 0 – 12 months of age

Treatment: The recommended treatment dose for infants 0 - 12 months of age is 3 mg/kg twice daily. This is based upon pharmacokinetic and safety data indicating that this dose in infants 0 - 12 months 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 5.2). The following dosing regimen is recommended for treatment of infants 0 - 12 months of age:

Body weight*	**Recommended dose for 5 days**
3 kg	9 mg twice daily
4 kg	12 mg twice daily
5 kg	15 mg twice daily
6 kg	18 mg twice daily
7 kg	21 mg twice daily
8 kg	24 mg twice daily
9 kg	27 mg twice daily
10 kg	30 mg 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.

Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Post-exposure prevention: The recommended prophylaxis dose for infants less than 1 year of age during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical data in infants and children 1 year of age or older and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza. The following age-adjusted dosing prophylaxis regimen is recommended for infants 0 - 12 months of age:

Age	**Recommended dose for 10 days**
0 - 12 months	3 mg/kg once daily

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Prevention during an influenza epidemic in the community: Prevention during an influenza epidemic has not been studied in children 0-12 months of age.

For instructions on preparing the extemporaneous formulation, see section 6.6.

Special populations

Hepatic impairment

No dose adjustment is required either for treatment or for prevention in patients with hepatic dysfunction. No studies have been carried out in paediatric patients with hepatic disorder.

Renal impairment
Treatment of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) twice daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) once daily
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) single dose

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

Prevention of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for prevention
> 60 (ml/min)	75 mg once daily
> 30 to60 (ml/min)	30 mg (suspension or capsules) once daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) every second day
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after every second haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) once weekly

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

There is insufficient clinical data available in infants and children (12 years of age and younger) with renal impairment to be able to make any dosing recommendation.

Older people
No dose adjustment is required, unless there is evidence of moderate or severe renal impairment.

Immunocompromised patients
Longer duration of seasonal prophylaxis up to 12 weeks has been evaluated in immunocompromised patients (see sections 4.4, 4.8 and 5.1).

Method of administration
Oral use.
Patients who are unable to swallow capsules may receive appropriate doses of Tamiflu suspension.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses (see section 5.1).

Tamiflu is not a substitute for influenza vaccination. Use of Tamiflu must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as

Tamiflu is administered. Tamiflu should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community. Susceptibility of circulating influenza virus strains to oseltamivir has been shown to be highly variable (see section 5.1). Therefore, prescribers should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use Tamiflu.

Severe concomitant condition
No information is available regarding the safety and efficacy of oseltamivir in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalisation.

Immunocompromised patients
The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established (see section 5.1).

Cardiac / respiratory disease
Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see section 5.1).

Paediatric population
No data allowing a dose recommendation for premature children (<36 weeks post-conceptual age) are currently available.

Severe renal impairment
Dose adjustment is recommended for both treatment and prevention in adolescents (13 to 17 years of age) and adults with severe renal impairment. There is insufficient clinical data available in infants and children (1 year of age or older) with renal impairment to be able to make any dosing recommendation (see sections 4.2 and 5.2).

Neuropsychiatric events
Neuropsychiatric events have been reported during administration of Tamiflu in patients with influenza, especially in children and adolescents. These events are also experienced by patients with influenza without oseltamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see section 5.2), suggest that clinically significant drug interactions via these mechanisms are unlikely.

Probenecid
No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

Amoxicillin
Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that oseltamivir interaction with this pathway is weak.

Renal elimination
Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Additional information
No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetylsalicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), rimantadine or warfarin (in subjects stable on warfarin and without influenza).

4.6 Fertility, pregnancy and lactation

Pregnancy
While no controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, there is limited data available from post-marketing and retrospective observational surveillance reports. These data in conjunction with animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see section 5.3). Pregnant women may receive Tamiflu, after considering the available safety information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

Breastfeeding
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 subtherapeutic dose to the infant. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the breastfeeding woman, administration of oseltamivir may be considered, where there are clear potential benefits to breastfeeding mothers.

Fertility
Based on preclinical data, there is no evidence that Tamiflu has an effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Tamiflu is based on data from 6049 adult/adolescent and 1473 paediatric patients treated with Tamiflu or placebo for influenza, and on data from 3990 adult/adolescent and 253 paediatric patients receiving Tamiflu or placebo/no treatment for the prophylaxis of influenza in clinical trials. In addition, 475 immunocompromised patients (including 18 children, of these 10 Tamiflu and 8 placebo) received Tamiflu or placebo for the prophylaxis of influenza.

In adults/adolescents, the most commonly reported adverse reactions (ARs) were nausea and vomiting in the treatment studies, and nausea in the prevention studies. The majority of these ARs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. In children, the most commonly reported adverse reaction was vomiting. In the majority of patients, these ARs did not lead to discontinuation of Tamiflu.

The following serious adverse reactions have been rarely reported since oseltamivir has been marketed: Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders.
(Regarding neuropsychiatric disorders, see section 4.4.)

Tabulated list of adverse reactions
The ARs listed in the tables below fall into the following categories: 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*), and very rare (< *1/10,000*). ARs are added to the appropriate category in the tables according to the pooled analysis from clinical studies.

Treatment and prevention of influenza in adults and adolescents:
In adult/adolescent treatment and prevention studies, ARs that occurred the most frequently at the recommended dose (75 mg bid for 5 days for treatment and 75 mg od for up to 6 weeks for prophylaxis) are shown in Table 1.

The safety profile reported in subjects who 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, despite a longer duration of dosing in the prophylaxis studies.

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 arrhythmia	
Respiratory, thoracic and mediastinal disorders		Cough, Sore throat, Rhinorrhea		

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
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 prevention of influenza in children:

A total of 1473 children (including otherwise healthy children aged 1-12 years old and asthmatic children aged 6-12 years old) participated in clinical studies of oseltamivir given for the treatment of influenza. Of those, 851 children received treatment with oseltamivir suspension. A total of 158 children received the recommended dose of Tamiflu once daily in a post-exposure prophylaxis study in households (n = 99), a 6-week paediatric seasonal prophylaxis study (n = 49) and a 12-week paediatric seasonal prophylaxis study in immunocompromised subjects (n = 10).

Table 2 shows the most frequently reported ARs from paediatric clinical trials.

Table 2 Adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg o.d.])

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Otitis media,		
Nervous system disorders		Headache		
Eye disorders:		Conjunctivitis (including red eyes, eye discharge and eye pain)		
Ear and labyrinth disorders:		Earache	Tympanic membrane disorder	
Respiratory, thoracic and mediastinal disorders	Cough, Nasal congestion	Rhinorrhoea		
Gastrointestinal disorders	Vomiting	Abdominal pain (incl. upper abdominal pain), Dyspepsia, Nausea		
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)	

Description of selected adverse reactions

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

In patients with influenza who were receiving Tamiflu, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases resulting in self-injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. 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.

Hepato-biliary disorders
Hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.

Other special populations

Paediatric population (infants less than one year of age)
In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of oseltamivir therapy in 135 influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrohea and diaper rash being the most frequently reported

adverse events (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 oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies (comprising together more than 2,400 infants of that age class), epidemiological databases research and postmarketing reports suggest that the safety profile in infants less than one year of age is similar to the established safety profile of children aged one year and older.

Older people and patients with chronic cardiac and/or respiratory disease
The population included in the influenza treatment studies is comprised of otherwise healthy adults/adolescents and patients “at risk” (patients at higher risk of developing complications associated with influenza, e.g. older people 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.

Immunocompromised patients
In a 12-week prophylaxis study in 475 immunocompromised patients, including 18 children 1 to 12 years of age and older, the safety profile in the 238 patients who received oseltamivir was consistent with that previously observed in Tamiflu prophylaxis clinical studies.

Children with pre-existing bronchial asthma
In general, the adverse reaction profile in children with pre-existing bronchial asthma was qualitatively similar to that of otherwise healthy children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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 4.8 Undesirable effects.

No specific antidote is known.

Paediatric population
Overdose has been reported more frequently for children than adults and adolescents. Caution should be exercised when preparing Tamiflu oral suspension and when administering Tamiflu products to children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors ATC code: J05AH02

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into

uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published studies.

Clinical studies

Treatment of influenza infection

The indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A.

Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population, which included both influenza-positive and -negative subjects (ITT), primary efficacy was reduced proportionally to the number of influenza-negative individuals. In the overall treatment population, influenza infection was confirmed in 67 % (range 46 % to 74 %) of the recruited patients. Of the older subjects, 64 % were influenza-positive and of those with chronic cardiac and/or respiratory disease 62 % were influenza-positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents 13 years of age and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥ 37.8 °C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2,413) enrolled into treatment studies, oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95 % CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95 % CI 4.0 – 4.4 days; $p \leq 0.0001$).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1,063) in the placebo group to 8.6 % (116/1,350) in the oseltamivir treated population ($p = 0.0012$).

Treatment of influenza in high risk populations: The median duration of influenza illness in older subjects (≥ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In influenza-positive older people, oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics from 19 % (52/268) in the placebo group to 12 % (29/250) in the oseltamivir treated population ($p = 0.0156$).

In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17 % (22/133) in the placebo group and 14 % (16/118) in the oseltamivir treated population ($p = 0.5976$).

Treatment of influenza in children: In a study of otherwise healthy children (65 % influenza-positive) aged 1 to 12 years (mean age 5.3 years) who had fever (≥ 37.8 °C) plus either cough or coryza, 67 % of influenza-positive patients were infected with influenza A and 33 % with influenza B. Oseltamivir treatment, started within 48 hours of onset of symptoms, significantly reduced the time to freedom from illness (defined as the simultaneous return to normal health and activity and alleviation of fever,

cough and coryza) by 1.5 days (95 % CI 0.6 – 2.2 days; $p < 0.0001$) compared to placebo. Oseltamivir reduced the incidence of acute otitis media from 26.5 % (53/200) in the placebo group to 16 % (29/183) in the oseltamivir treated children ($p = 0.013$).

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) FEV_1 had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo ($p = 0.0148$) in this population.

The European Medicines Agency has deferred the obligation to submit the results of studies with Tamiflu in one or more subsets of the paediatric population in influenza. See section 4.2 for information on paediatric use.

The indication in infants below the age of 1 is based upon extrapolation of efficacy data from older children and the recommended posology is based upon pharmacokinetic modelling data (see Section 5.2).

Treatment of influenza B infection: Overall, 15 % of the influenza-positive population were infected by influenza B, proportions ranging from 1 to 33 % in individual studies. The median duration of illness in influenza B infected subjects did not differ significantly between the treatment groups in individual studies. Data from 504 influenza B infected subjects were pooled across all studies for analysis. Oseltamivir reduced the time to alleviation of all symptoms by 0.7 days (95 % CI 0.1 – 1.6 days; $p = 0.022$) and the duration of fever (≥ 37.8 °C), cough and coryza by one day (95 % CI 0.4 – 1.7 days; $p < 0.001$) compared to placebo.

Prevention of influenza
The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory-confirmed influenza. The virulence of influenza epidemics is not predictable and varies within a region and from season to season, therefore the number needed to treat (NNT) in order to prevent one case of influenza illness varies.

Post-exposure prevention: In a study in contacts (12.6 % vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily was started within 2 days of onset of symptoms in the index case and continued for seven days. Influenza was confirmed in 163 out of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12 %) in the placebo group to 2/205 (1 %) in the oseltamivir group (92 % reduction [95 % CI 6 – 16; $p \leq 0.0001$]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95 % CI 9 – 12) and was 16 (95 % CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and 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 the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20 % (27/136) in the group not receiving prevention to 7 % (10/135) in the group receiving prevention (62.7 % reduction [95 % CI 26.0 – 81.2; $p = 0.0042$]). In households of influenza-infected index cases, there was a reduction in the incidence of influenza from 26 % (23/89) in the group not receiving prevention to 11 % (9/84) in the group receiving prevention (58.5 % reduction [95 % CI 15.6 – 79.6; $p = 0.0114$]).
According to subgroup analysis in children at 1 to 12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21/111) in the group not receiving prevention to 7 % (7/104) in the group receiving prevention (64.4 % reduction [95 % CI 15.8 – 85.0; $p = 0.0188$]). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15/70) in the group

not receiving prevention to 4 % (2/47) in the group receiving prevention (80.1 % reduction [95 % CI 22.0 – 94.9; p = 0.0206]). The NNT for the total paediatric population was 9 (95 % CI 7 – 24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTII), respectively.

Prevention during an influenza epidemic in the community: In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25/519 (4.8 %) in the placebo group to 6/520 (1.2 %) in the oseltamivir group (76 % reduction [95 % CI 1.6 – 5.7; p = 0.0006]) during a community outbreak of influenza. The NNT in this study was 28 (95 % CI 24 – 50).
A study in older people in nursing homes, where 80 % of participants received vaccine in the season of the study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4 %) in the placebo group to 1/276 (0.4 %) in the oseltamivir group (92 % reduction [95 % CI 1.5 – 6.6; p = 0.0015]). The NNT in this study was 25 (95 % CI 23 – 62).

Prophylaxis of influenza in immunocompromised patients: A double-blind, placebo-controlled, randomised study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised patients (388 patients with solid organ transplantation [195 placebo; 193 oseltamivir], 87 patients with haemopoetic stem cell transplantation [43 placebo; 44 oseltamivir], no patient with other immunosuppressant conditions), including 18 children 1 to 12 years of age. The primary endpoint in this study was the incidence of laboratory-confirmed clinical influenza as determined by viral culture and/or a four-fold rise in HAI antibodies. The incidence of laboratory-confirmed clinical influenza was 2.9 % (7/238) in the placebo group and 2.1 % (5/237) in the oseltamivir group (95 % CI -2.3 % – 4.1 %; p = 0.772).

Specific studies have not been conducted to assess the reduction in the risk of complications.

Oseltamivir 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. All patients who were found to carry oseltamivir-resistant virus did so transiently, cleared the virus normally and showed no clinical deterioration.

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	Geno- and Phenotyping*
Adults and adolescents	4/1,245 (0.32 %)	5/1,245 (0.4 %)
Children (1-12 years)	19/464 (4.1 %)	25/464 (5.4 %)

* Full genotyping was not performed in all studies.

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. Resistant strains selected during oseltamivir treatment have been isolated from both immunocompetent and immunocompromised patients. Immunocompromised patients and young children are at a higher risk of developing oseltamivir-resistant virus during treatment.

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. Since 2007 resistance associated H275Y mutation in seasonal H1N1 strains has become widespread. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. In 2008, H275Y was found in > 99 % of circulating H1N1 influenza isolates in Europe. The 2009 H1N1

influenza (“swine flu”) was almost uniformly susceptible to oseltamivir, with only sporadic reports of resistance in connection with both therapeutic and prophylactic regimens.

5.2 Pharmacokinetic properties

General Information

Absorption
Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5 % relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution
The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate distributes to all sites of influenza virus spread.

The binding of the oseltamivir carboxylate to human plasma protein is negligible (approximately 3 %).

Biotransformation
Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In vitro* studies demonstrated that neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination
Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds glomerular filtration rate (7.5 l/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Other special populations

Paediatric population
Infants less than 1 year of age:
The pharmacokinetics, pharmacodynamics and safety of Tamiflu have been evaluated in two uncontrolled open-label studies including influenza infected children less than one year of age (n=135). 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 infants 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 (see sections 4.1 and 4.2).The reported adverse events were consistent with the established safety profile in older children.

There are no data available for infants below 1 year of age for post exposure prevention of influenza. Prevention during an influenza epidemic in the community has not been studied in children below 12 years of age.

Infants and children 1 year of age or older: The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in infants, children and adolescents 1 to 16 years of age. Multiple-dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the pro-drug and its active metabolite faster than adults,

resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older are similar to those in adults.

Older people
Exposure to the active metabolite at steady state was 25 to 35 % higher in older people (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in older people were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for older people unless there is evidence of moderate or severe renal impairment (creatinine clearance below 60 ml /min) (see section 4.2).

Renal impairment
Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see section 4.2.

Hepatic impairment
In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of Tamiflu in its adopted therapeutic indications.

Teratology studies have been conducted in rats and rabbits at doses of up to 1,500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal development were observed. A rat fertility study up to a dose of 1,500 mg/kg/day demonstrated no adverse reactions on either sex. In pre- and post-natal rat studies, prolonged parturition was noted at 1,500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in 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 sensitisation to oseltamivir was observed in a "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active substance showed erythema after challenging the induced animals. Reversible irritancy of rabbits' eyes was detected.

Whereas very high oral single doses of oseltamivir phosphate salt, up to the highest dose tested (1,310 mg/kg), had no adverse reactions in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These reactions were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse reactions were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days post partum).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core
Pregelatinised starch (derived from maize starch)
Talc
Povidone
Croscarmellose sodium
Sodium stearyl fumarate

Capsule shell
Gelatin
Yellow iron oxide (E172)
Red iron oxide (E172)
Black iron oxide (E172)
Titanium dioxide (E171)

Printing ink
Shellac
Titanium dioxide (E171)
FD and C Blue 2 (indigo carmine, E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

10 years

Storage of the pharmacy compounded suspension
Shelf life of 10 days when stored below 25 °C.

6.4 Special precautions for storage

Do not store above 25 °C.

For storage conditions of the pharmacy compounded suspension, see section 6.3.

6.5 Nature and contents of container

Triplex blister pack (PVC/PE/PVDC, sealed with aluminium foil).
Pack-size 10 capsules.

6.6 Special precautions for disposal and other handling

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

Extemporaneous formulation

When Tamiflu powder for oral suspension is not available
Commercially manufactured Tamiflu for oral suspension (6 mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. In the event that commercially manufactured Tamiflu powder for oral suspension is not available, the pharmacist may compound a suspension (6 mg/ml) from Tamiflu capsules or patients can prepare the suspension from capsules at home.

The pharmacy preparation should be preferred to home preparation. Detailed information on the home preparation can be found in the package leaflet of Tamiflu capsules under “Making liquid Tamiflu at home”.

Syringes of appropriate volume and grading should be provided for administering the pharmacy compounded suspension as well as for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the syringes.

Pharmacy compounding

Pharmacy compounded 6 mg/ml suspension prepared from capsules

Adults, adolescents and infants and children 1 year of age or older who are unable to swallow intact capsules
This procedure describes the preparation of a 6 mg/ml suspension that will provide one patient with enough medicine for a 5-day course of treatment or a 10-day course of prophylaxis.

The pharmacist may compound a 6 mg/ml suspension 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 to provide a 5-day course of treatment or a 10-day course of prophylaxis for the patient. The total volume required is determined by the weight of the patient according to the recommendation in the table below. To allow for accurate volume withdrawal of up to 10 doses (2 withdrawals per daily treatment dose for 5 days), the column indicating measurement loss is to be considered for compounding.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient’s weight

Body weight (kg)	**Total volume to compound per patient weight (ml) Measurement loss not considered**	**Total volume to compound per patient weight (ml) Measurement loss considered**
10 kg to 15 kg	50 ml	60 ml or 75 ml*
> 15 kg to 23 kg	75 ml	90 ml or 100 ml*
> 23 kg to 40 kg	100 ml	125 ml
> 40 kg	125 ml	137.5 ml (or 150 ml)*

* Depending on the capsule strength used.

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) of pharmacy compounded 6 mg/ml suspension as shown in the table below:

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension

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	
60 ml	Please use alternative capsule strength*	8 capsules (360 mg)	12 capsules (360 mg)	59.5 ml
75 ml	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	74 ml
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
125 ml	10 capsules (750 mg)	Please use alternative capsule strength*	25 capsules (750 mg)	123.5 ml
137.5 ml	11 capsules (825 mg)	Please use alternative capsule strength*	Please use alternative capsule strength*	136 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

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

1. In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
2. Open the stated amount of Tamiflu capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.
3. With a suitable stirring device, stir for 2 minutes.
   (Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Tamiflu capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Close the bottle using a child-resistant cap.
6. Put an ancillary label on the bottle indicating “Shake Gently Before Use”.
   (Note: This compounded suspension should be gently shaken prior to administration to minimise the tendency for air entrapment.)
7. Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date label according to storage condition (see section 6.3).

Place a pharmacy label on the bottle that includes the patient’s name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.

Dosing chart for pharmacy-compounded 6 mg/ml suspension prepared from Tamiflu capsules for infants and children 1 year of age or older

Body weight (kg)	Dose (mg)	Volume per dose 6 mg/ml	Treatment dose (for 5 days)	Prophylaxis dose (for 10 days)
10 kg to 15 kg	30 mg	5 ml	5 ml twice daily	5 ml once daily
> 15 kg to 23 kg	45 mg	7.5 ml	7.5 ml twice daily	7.5 ml once daily
> 23 kg to 40 kg	60 mg	10 ml	10 ml twice daily	10 ml once daily
> 40 kg	75 mg	12.5 ml	12.5 ml twice daily	12.5 ml once daily

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing table above) on the oral syringe for each patient.

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

Infants less than 1 year of age

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 or a 10-day course of prophylaxis.

The pharmacist may compound a 6 mg/ml suspension 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. To allow for accurate volume withdrawal of up to 10 doses (2 withdrawals per daily treatment dose for 5 days), the column indicating measurement loss is to be considered for compounding.

Volume of pharmacy compounded 6 mg/ml suspension prepared based upon the patient's weight

Body weight (kg)	Total volume to compound per patient weight (ml) Measurement loss not considered	Total volume to compound per patient weight (ml) Measurement loss considered
≤ 7 kg	up to 40 ml	50 ml
> 7 kg to 10 kg	50 ml	60 ml or 75 ml*

* Depending on the capsule strength used.

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) of pharmacy compounded 6 mg/ml suspension as shown in the table below:

Number of capsules and amount of vehicle needed to prepare the total volume of a pharmacy compounded 6 mg/ml suspension

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	
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)	59.5 ml
75 ml	6 capsules (450 mg)	10 capsules (450 mg)	15 capsules (450 mg)	74 ml

* There is no combination of this capsule strength that can be used to achieve the target concentration; therefore, please use an alternative capsule strength.

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

1. In a glass beaker of suitable size place the stated amount of water containing 0.05 % w/v sodium benzoate added as a preservative.
2. Open the stated amount of Tamiflu capsules and transfer the content of each capsule directly to the preserved water in the glass beaker.
3. With a suitable stirring device, stir for 2 minutes.
   (Note: The drug substance, oseltamivir phosphate, readily dissolves in water. The suspension is caused by some of the excipients of Tamiflu capsules, which are insoluble.)
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Close the bottle using a child-resistant cap.
6. Put an ancillary label on the bottle indicating “Shake Gently Before Use”.
   (Note: This compounded suspension should be gently shaken prior to administration to minimise the tendency for air entrapment.)
7. Instruct the parent or caregiver that any remaining material following completion of therapy must be discarded. It is recommended that this information be provided by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
8. Place an appropriate expiration date label according to storage condition (see section 6.3).

Place a pharmacy label on the bottle that includes the patient’s name, dosing instructions, use by date, name of medicinal product and any other required information to be in compliance with local pharmacy regulations. Refer to the table below for the proper dosing instructions.

Dosing chart for pharmacy compounded 6 mg/ml suspension prepared from Tamiflu capsules for infants less than 1 year of age

Body Weight (rounded to the nearest 0.5 kg)	Dose (mg)	Volume per dose (6 mg/ml)	Treatment Dose (for 5 days)	Prophylaxis Dose (for 10 days)	Dispenser size to use (grading 0.1 ml)
3 kg	9 mg	1.5 ml	1.5 ml twice daily	1.5 ml once daily	2.0 ml or 3.0 ml
3.5 kg	10.5 mg	1.8 ml	1.8 ml twice daily	1.8 ml once daily	2.0 ml or 3.0 ml
4 kg	12 mg	2.0 ml	2.0 ml twice daily	2.0 ml once daily	3.0 ml
4.5 kg	13.5 mg	2.3 ml	2.3 ml twice daily	2.3 ml once daily	3.0 ml
5 kg	15 mg	2.5 ml	2.5 ml twice daily	2.5 ml once daily	3.0 ml
5.5 kg	16.5 mg	2.8 ml	2.8 ml twice daily	2.8 ml once daily	3.0 ml
6 kg	18 mg	3.0 ml	3.0 ml twice daily	3.0 ml once daily	3.0 ml (or 5.0 ml)
6.5 kg	19.5 mg	3.3 ml	3.3 ml twice daily	3.3 ml once daily	5.0 ml
7 kg	21 mg	3.5 ml	3.5ml twice daily	3.5 ml once daily	5.0 ml
7.5 kg	22.5 mg	3.8 ml	3.8 ml twice daily	3.8 ml once daily	5.0 ml
8 kg	24 mg	4.0 ml	4.0 ml twice daily	4.0 ml once daily	5.0 ml
8.5 kg	25.5 mg	4.3 ml	4.3 ml twice daily	4.3 ml once daily	5.0 ml
9 kg	27 mg	4.5 ml	4.5 ml twice daily	4.5 ml once daily	5.0 ml
9.5 kg	28.5 mg	4.8 ml	4.8 ml twice daily	4.8 ml once daily	5.0 ml
10 kg	30 mg	5.0 ml	5.0 ml twice daily	5.0 ml once daily	5.0 ml

Dispense the pharmacy compounded suspension with a graduated oral syringe for measuring small amounts of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (according to the dosing tables above) on the oral syringe for each patient.

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

Home preparation

When commercially manufactured Tamiflu oral suspension is not available, a pharmacy compounded suspension prepared from Tamiflu capsules must be used (see detailed instructions above). If the commercially manufactured Tamiflu oral suspension and the pharmacy compounded suspension is also not available, Tamiflu suspension may be prepared at home.

When appropriate capsule strengths are available for the dose needed, the dose is given by opening the capsule and mixing its contents with no more than one teaspoon of a suitable sweetened food product. The bitter taste can be masked by products such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce). 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, the preparation of Tamiflu suspension involves additional steps. Detailed instructions can be found in the package leaflet of Tamiflu capsules under “Making liquid Tamiflu at home”.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2002
Date of last renewal: 20 June 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 6 mg/ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of reconstituted suspension contains oseltamivir phosphate equivalent to 6 mg of oseltamivir.
One bottle of reconstituted suspension (65 ml) contains 390 mg of oseltamivir.

Excipients with known effect:
5 ml oseltamivir suspension delivers 0.9 g of sorbitol.
7.5 ml oseltamivir suspension delivers 1.3 g of sorbitol.
10 ml oseltamivir suspension delivers 1.7 g of sorbitol.
12.5 ml oseltamivir suspension delivers 2.1 g of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension
The powder is a granulate or clumped granulate with a white to light yellow colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza
Tamiflu is indicated 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 two days of first onset of symptoms.

Prevention of influenza
- Post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

- The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.

- Tamiflu is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).

Tamiflu is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations (see section 5.1).

4.2 Posology and method of administration

Posology

Tamiflu suspension and Tamiflu hard capsules are bioequivalent formulations. 75 mg doses can be administered as either

- one 75 mg capsule or
- one 30 mg capsule plus one 45 mg capsule or
- by administering one 30 mg dose plus one 45 mg dose of suspension.

Adults, adolescents or children (> 40 kg) who are able to swallow capsules may receive appropriate doses of Tamiflu capsules.

Treatment
Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

For adolescents (13 to 17 years of age) and adults: The recommended oral dose is 75 mg oseltamivir twice daily for 5 days.

Paediatric population

For infants and children1 year of age or older: The recommended dose of Tamiflu 6 mg/ml oral suspension is indicated in the table below. Tamiflu 30 mg and 45 mg capsules are available as an alternative to the recommended dose of Tamiflu 6 mg/ml suspension.

The following weight-adjusted dosing regimens are recommended for infants and children 1 year of age or older:

Body weight	Recommended dose for 5 days	Amount of oral suspension to withdraw
10 kg to 15 kg	30 mg twice daily	5 ml twice daily
> 15 kg to 23 kg	45 mg twice daily	7.5 ml twice daily
> 23 kg to 40 kg	60 mg twice daily	10 ml twice daily
> 40 kg	75 mg twice daily	12.5 ml twice daily

Children weighing > 40 kg and who are able to swallow capsules may receive treatment with the adult dosage of 75 mg capsules twice daily for 5 days as an alternative to the recommended dose of Tamiflu suspension.

For infants less than 1 year of age: The recommended treatment dose for infants 0 - 12 months of age is 3 mg/kg twice daily. This is based upon pharmacokinetic and safety data indicating that this dose in infants 0 - 12 months 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 5.2).

A 3 ml oral dispenser (graduated in 0.1 ml steps) should be used for dosing children 0 - 12 months of age requiring 1 ml to 3 ml of Tamiflu 6 mg/ml oral suspension. For higher doses the 10 ml syringe should be used. The following dosing regimen is recommended for treatment of infants below 1 year of age:

Dosing table of oseltamivir for children less than 1 year of age : 3 mg/kg twice daily

Body Weight*	Recommended dose for 5 days	Amount of oral suspension to withdraw	Dispenser size to use
3 kg	9 mg twice daily	1.5 ml twice daily	3 ml
3.5 kg	10.5 mg twice daily	1.8 ml twice daily	3 ml
4 kg	12 mg twice daily	2.0 ml twice daily	3 ml
4.5 kg	13.5 mg twice daily	2.3 ml twice daily	3 ml
5 kg	15 mg twice daily	2.5 ml twice daily	3 ml
5.5 kg	16.5 mg twice daily	2.8 ml twice daily	3 ml
6 kg	18 mg twice daily	3.0 ml twice daily	3 ml
> 6 - 7 kg	21 mg twice daily	3.5 ml twice daily	10 ml
> 7 - 8 kg	24 mg twice daily	4.0 ml twice daily	10 ml
> 8 - 9 kg	27 mg twice daily	4.5 ml twice daily	10 ml
> 9 - 10 kg	30 mg twice daily	5.0 ml twice daily	10 ml

* This table is not intended to contain all possible weights for this population.

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Prevention

Post-exposure prevention

For adolescents (13 to 17 years of age) and adults: The recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days. Therapy should begin as soon as possible within two days of exposure to an infected individual.

For infants and children 1 year of age or older: Tamiflu 30 mg and 45 mg capsules are available as an alternative to the recommended dose of Tamiflu 6 mg/ml suspension.

The recommended post-exposure prevention dose of Tamiflu is:

Body weight	Recommended dose for 10 days	Amount of oral suspension to withdraw
10 kg to 15 kg	30 mg once daily	5 ml once daily
> 15 kg to 23 kg	45 mg once daily	7.5 ml once daily
> 23 kg to 40 kg	60 mg once daily	10 ml once daily
> 40 kg	75 mg once daily	12.5 ml once daily

Children weighing > 40 kg and who are able to swallow capsules may receive prophylaxis with a 75 mg capsule once daily for 10 days as an alternative to the recommended dose of Tamiflu suspension.

For infants less than 1 year of age: The recommended prophylaxis dose for infants less than 12 months during a pandemic influenza outbreak is half of the daily treatment dose. This is based upon clinical data in children > 1 year of age and adults showing that a prophylaxis dose equivalent to half the daily treatment dose is clinically efficacious for the prevention of influenza.

In case of a pandemic, a 3 ml oral dispenser (graduated in 0.1 ml steps) should be used for dosing children below 1 year of age requiring 1 ml to 3 ml of Tamiflu 6 mg/ml oral suspension. For higher doses the 10 ml syringe should be used.

The following dosing regimen is recommended for infants less than 1 year of age:

Dosing table of oseltamivir for children below one year of age : 3 mg/kg once daily

Body Weight*	Recommended dose for 10 days	Amount of oral suspension to withdraw	Dispenser size to use
3 kg	9 mg once daily	1.5 ml once daily	3 ml
3.5 kg	10.5 mg once daily	1.8 ml once daily	3 ml
4 kg	12 mg once daily	2.0 ml once daily	3 ml
4.5 kg	13.5 mg once daily	2.3 ml once daily	3 ml
5 kg	15 mg once daily	2.5 ml once daily	3 ml
5.5 kg	16.5 mg once daily	2.8 ml once daily	3 ml
6 kg	18 mg once daily	3.0 ml once daily	3 ml
> 6 - 7 kg	21 mg once daily	3.5 ml once daily	10 ml
> 7 - 8 kg	24 mg once daily	4.0 ml once daily	10 ml
> 8 - 9 kg	27 mg once daily	4.5 ml once daily	10 ml
> 9 - 10 kg	30 mg once daily	5.0 ml once daily	10 ml

* This table is not intended to contain all possible weights for this population.

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Prevention during an influenza epidemic in the community
Prevention during an influenza epidemic has not been studied in children below 12 years of age. The recommended dose for adults and adolescents for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to 6 weeks.

Special populations

Hepatic impairment
No dose adjustment is required either for treatment or for prevention in patients with hepatic dysfunction. No studies have been carried out in paediatric patients with hepatic disorder.

Renal impairment
Treatment of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) twice daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) once daily
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) single dose

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

Prevention of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for prevention
> 60 (ml/min)	75 mg once daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) once daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) every second day
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after every second haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) once weekly

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

There is insufficient clinical data available in infants and children (12 years of age and younger) with renal impairment to be able to make any dosing recommendation.

Older people
No dose adjustment is required, unless there is evidence of moderate or severe renal impairment.

Immunocompromised patients
Longer duration of seasonal prophylaxis up to 12 weeks has been evaluated in immunocompromised patients (see sections 4.4, 4.8 and 5.1).

Method of administration
For dosing, a 3 ml and 10 ml oral dispenser is provided in the box.
It is recommended that Tamiflu powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses (see section 5.1).

Tamiflu is not a substitute for influenza vaccination. Use of Tamiflu must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as Tamiflu is administered. Tamiflu should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community. Susceptibility of circulating influenza virus strains to oseltamivir has been shown to be highly variable (see section 5.1). Therefore, prescribers should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use Tamiflu.

Severe concomitant condition
No information is available regarding the safety and efficacy of oseltamivir in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalisation.

Immunocompromised patients
The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established (see section 5.1).

Cardiac / respiratory disease
Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see section 5.1).

Paediatric population
No data allowing a dose recommendation for premature children (<36 weeks post-conceptual age) are currently available.

Severe renal impairment
Dose adjustment is recommended for both treatment and prevention in adolescents (13 to 17 years of age) and adults with severe renal impairment. There is insufficient clinical data available in infants and children (1 year of age or older) with renal impairment to be able to make any dosing recommendation (see sections 4.2 and 5.2).

Neuropsychiatric events
Neuropsychiatric events have been reported during administration of Tamiflu in patients with influenza, especially in children and adolescents. These events are also experienced by patients with influenza without oseltamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8).

This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
Sorbitol can have a mild laxative effect.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see section 5.2), suggest that clinically significant drug interactions via these mechanisms are unlikely.

Probenecid
No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

Amoxicillin
Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that oseltamivir interaction with this pathway is weak.

Renal elimination
Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Additional information
No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetylsalicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), rimantadine or warfarin (in subjects stable on warfarin and without influenza).

4.6 Fertility, pregnancy and lactation

Pregnancy
While no controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, there is limited data available from post-marketing and retrospective observational surveillance reports. These data in conjunction with animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see section 5.3). Pregnant women may receive Tamiflu, after considering the available safety information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

Breastfeeding
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 subtherapeutic dose to the infant. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the breastfeeding woman, administration of oseltamivir may be considered, where there are clear potential benefits to breastfeeding mothers.

Fertility
Based on preclinical data, there is no evidence that Tamiflu has an effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Tamiflu is based on data from 6049 adult/adolescent and 1473 paediatric patients treated with Tamiflu or placebo for influenza, and on data from 3990 adult/adolescent and 253 paediatric patients receiving Tamiflu or placebo/no treatment for the prophylaxis of influenza in clinical trials. In addition, 475 immunocompromised patients (including 18 children, of these 10 Tamiflu and 8 placebo) received Tamiflu or placebo for the prophylaxis of influenza.

In adults/adolescents, the most commonly reported adverse reactions (ARs) were nausea and vomiting in the treatment studies, and nausea in the prevention studies. The majority of these ARs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. In children, the most commonly reported adverse reaction was vomiting. In the majority of patients, these ARs did not lead to discontinuation of Tamiflu.

The following serious adverse reactions have been rarely reported since oseltamivir has been marketed: Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders.
(Regarding neuropsychiatric disorders, see section 4.4.)

Tabulated list of adverse reactions
The ARs listed in the tables below fall into the following categories: 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*), and very rare (< *1/10,000*). ARs are added to the appropriate category in the tables according to the pooled analysis from clinical studies.

Treatment and prevention of influenza in adults and adolescents:
In adult/adolescent treatment and prevention studies, ARs that occurred the most frequently at the recommended dose (75 mg bid for 5 days for treatment and 75 mg od for up to 6 weeks for prophylaxis) are shown in Table 1.

The safety profile reported in subjects who 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, despite a longer duration of dosing in the prophylaxis studies.

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 arrhythmia	
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

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
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 prevention of influenza in children:

A total of 1473 children (including otherwise healthy children aged 1-12 years old and asthmatic children aged 6-12 years old) participated in clinical studies of oseltamivir given for the treatment of influenza. Of those, 851 children received treatment with oseltamivir suspension. A total of 158 children received the recommended dose of Tamiflu once daily in a post-exposure prophylaxis study in households (n = 99), a 6-week paediatric seasonal prophylaxis study (n = 49) and a 12-week paediatric seasonal prophylaxis study in immunocompromised subjects (n = 10).

Table 2 shows the most frequently reported ARs from paediatric clinical trials.

Table 2 Adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg o.d.])

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Otitis media,		
Nervous system disorders		Headache		
Eye disorders:		Conjunctivitis (including red eyes, eye discharge and eye pain)		
Ear and labyrinth disorders:		Earache	Tympanic membrane disorder	
Respiratory, thoracic and mediastinal disorders	Cough, Nasal congestion	Rhinorrhoea		
Gastrointestinal disorders	Vomiting	Abdominal pain (incl. upper abdominal pain), Dyspepsia, Nausea		
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)	

Description of selected adverse reactions

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

In patients with influenza who were receiving Tamiflu, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases resulting in self-injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. 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.

Hepato-biliary disorders
Hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.

Other special populations

Paediatric population (infants less than one year of age)
In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of oseltamivir therapy in 135 influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrohea and diaper rash being the most frequently reported

adverse events (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 oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies (comprising together more than 2,400 infants of that age class), epidemiological databases research and postmarketing reports suggest that the safety profile in infants less than one year of age is similar to the established safety profile of children aged one year and older.

Older people and patients with chronic cardiac and/or respiratory disease
The population included in the influenza treatment studies is comprised of otherwise healthy adults/adolescents and patients “at risk” (patients at higher risk of developing complications associated with influenza, e.g. older people 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.

Immunocompromised patients
In a 12-week prophylaxis study in 475 immunocompromised patients, including 18 children 1 to 12 years of age and older, the safety profile in the 238 patients who received oseltamivir was consistent with that previously observed in Tamiflu prophylaxis clinical studies.

Children with pre-existing bronchial asthma
In general, the adverse reaction profile in children with pre-existing bronchial asthma was qualitatively similar to that of otherwise healthy children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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 4.8 Undesirable effects.

No specific antidote is known.

Paediatric population
Overdose has been reported more frequently for children than adults and adolescents. Caution should be exercised when preparing Tamiflu oral suspension and when administering Tamiflu products to children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors ATC code: J05AH02

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into

uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published studies.

Clinical studies

Treatment of influenza infection

The indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A.Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population, which included both influenza-positive and -negative subjects (ITT), primary efficacy was reduced proportionally to the number of influenza-negative individuals. In the overall treatment population, influenza infection was confirmed in 67 % (range 46 % to 74 %) of the recruited patients. Of the older subjects, 64 % were influenza-positive and of those with chronic cardiac and/or respiratory disease 62 % were influenza-positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents 13 years of age and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥ 37.8 °C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2,413) enrolled into treatment studies, oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95 % CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95 % CI 4.0 – 4.4 days; $p \leq 0.0001$).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1,063) in the placebo group to 8.6 % (116/1,350) in the oseltamivir treated population ($p = 0.0012$).

Treatment of influenza in high risk populations: The median duration of influenza illness in older subjects (≥ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In influenza-positive older people, oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics from 19 % (52/268) in the placebo group to 12 % (29/250) in the oseltamivir treated population ($p = 0.0156$).

In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17 % (22/133) in the placebo group and 14 % (16/118) in the oseltamivir treated population ($p = 0.5976$).

Treatment of influenza in children: In a study of otherwise healthy children (65 % influenza-positive) aged 1 to 12 years (mean age 5.3 years) who had fever (≥ 37.8 °C) plus either cough or coryza, 67 % of influenza-positive patients were infected with influenza A and 33 % with influenza B. Oseltamivir treatment, started within 48 hours of onset of symptoms, significantly reduced the time to freedom from illness (defined as the simultaneous return to normal health and activity and alleviation of fever,

cough and coryza) by 1.5 days (95 % CI 0.6 – 2.2 days; $p < 0.0001$) compared to placebo. Oseltamivir reduced the incidence of acute otitis media from 26.5 % (53/200) in the placebo group to 16 % (29/183) in the oseltamivir treated children ($p = 0.013$).

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) FEV_1 had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo ($p = 0.0148$) in this population.

The European Medicines Agency has deferred the obligation to submit the results of studies with Tamiflu in one or more subsets of the paediatric population in influenza. See section 4.2 for information on paediatric use.
The indication in infants below the age of 1 is based upon extrapolation of efficacy data from older children and the recommended posology is based upon pharmacokinetic modelling data (see Section 5.2).

Treatment of influenza B infection: Overall, 15 % of the influenza-positive population were infected by influenza B, proportions ranging from 1 to 33 % in individual studies. The median duration of illness in influenza B infected subjects did not differ significantly between the treatment groups in individual studies. Data from 504 influenza B infected subjects were pooled across all studies for analysis. Oseltamivir reduced the time to alleviation of all symptoms by 0.7 days (95 % CI 0.1 – 1.6 days; $p = 0.022$) and the duration of fever (≥ 37.8 °C), cough and coryza by one day (95 % CI 0.4 – 1.7 days; $p < 0.001$) compared to placebo.

Prevention of influenza
The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory-confirmed influenza. The virulence of influenza epidemics is not predictable and varies within a region and from season to season, therefore the number needed to treat (NNT) in order to prevent one case of influenza illness varies.

Post-exposure prevention: In a study in contacts (12.6 % vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily was started within 2 days of onset of symptoms in the index case and continued for seven days. Influenza was confirmed in 163 out of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12 %) in the placebo group to 2/205 (1 %) in the oseltamivir group (92 % reduction [95 % CI 6 – 16; $p \leq 0.0001$]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95 % CI 9 – 12) and was 16 (95 % CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and 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 the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20 % (27/136) in the group not receiving prevention to 7 % (10/135) in the group receiving prevention (62.7 % reduction [95 % CI 26.0 – 81.2; $p = 0.0042$]). In households of influenza-infected index cases, there was a reduction in the incidence of influenza from 26 % (23/89) in the group not receiving prevention to 11 % (9/84) in the group receiving prevention (58.5 % reduction [95 % CI 15.6 – 79.6; $p = 0.0114$]).
According to subgroup analysis in children at 1 to 12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21/111) in the group not receiving prevention to 7 % (7/104) in the group receiving prevention (64.4 % reduction [95 % CI 15.8 – 85.0; $p = 0.0188$]). Among children who were not already shedding virus at baseline, the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15/70) in the group not receiving prevention to 4 % (2/47) in the group receiving prevention (80.1 % reduction [95 % CI

22.0 – 94.9; p = 0.0206]). The NNT for the total paediatric population was 9 (95 % CI 7 – 24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTII), respectively.

Prevention during an influenza epidemic in the community: In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25/519 (4.8 %) in the placebo group to 6/520 (1.2 %) in the oseltamivir group (76 % reduction [95 % CI 1.6 – 5.7; p = 0.0006]) during a community outbreak of influenza. The NNT in this study was 28 (95 % CI 24 – 50).
A study in older people in nursing homes, where 80 % of participants received vaccine in the season of the study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4 %) in the placebo group to 1/276 (0.4 %) in the oseltamivir group (92 % reduction [95 % CI 1.5 – 6.6; p = 0.0015]). The NNT in this study was 25 (95 % CI 23 – 62).

Prophylaxis of influenza in immunocompromised patients: A double-blind, placebo-controlled, randomised study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised patients (388 patients with solid organ transplantation [195 placebo; 193 oseltamivir], 87 patients with haemopoetic stem cell transplantation [43 placebo; 44 oseltamivir], no patient with other immunosuppressant conditions), including 18 children 1 to 12 years of age. The primary endpoint in this study was the incidence of laboratory-confirmed clinical influenza as determined by viral culture and/or a four-fold rise in HAI antibodies. The incidence of laboratory-confirmed clinical influenza was 2.9 % (7/238) in the placebo group and 2.1 % (5/237) in the oseltamivir group (95 % CI -2.3 % – 4.1 %; p = 0.772).

Specific studies have not been conducted to assess the reduction in the risk of complications.

Oseltamivir 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. All patients who were found to carry oseltamivir-resistant virus did so transiently, cleared the virus normally and showed no clinical deterioration.

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	Geno- and Phenotyping*
Adults and adolescents	4/1,245 (0.32 %)	5/1,245 (0.4 %)
Children (1-12 years)	19/464 (4.1 %)	25/464 (5.4 %)

* Full genotyping was not performed in all studies.

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. Resistant strains selected during oseltamivir treatment have been isolated from both immunocompetent and immunocompromised patients. Immunocompromised patients and young children are at a higher risk of developing oseltamivir-resistant virus during treatment.

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. Since 2007 resistance associated H275Y mutation in seasonal H1N1 strains has become widespread. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. In 2008, H275Y was found in > 99 % of circulating H1N1 influenza isolates in Europe. The 2009 H1N1

influenza (“swine flu”) was almost uniformly susceptible to oseltamivir, with only sporadic reports of resistance in connection with both therapeutic and prophylactic regimens.

5.2 Pharmacokinetic properties

General Information

Absorption
Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5 % relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution
The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate distributes to all sites of influenza virus spread.

The binding of the oseltamivir carboxylate to human plasma protein is negligible (approximately 3 %).

Biotransformation
Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In vitro* studies demonstrated that neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination
Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds glomerular filtration rate (7.5 l/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Other special populations

Paediatric population
Infants less than 1 year of age: The pharmacokinetics, pharmacodynamics and safety of Tamiflu have been evaluated in two uncontrolled open-label studies including influenza infected children less than one year of age (n=135). 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 infants 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 (see sections 4.1 and 4.2).The reported adverse events were consistent with the established safety profile in older children.

There are no data available for infants below 1 year of age for post exposure prevention of influenza. Prevention during an influenza epidemic in the community has not been studied in children below 12 years of age.

Infants and children 1 year of age or older: The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in infants, children and adolescents 1 to 16 years of age. Multiple-dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the pro-drug and its active metabolite faster than adults, resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate

exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older are similar to those in adults.

Older people
Exposure to the active metabolite at steady state was 25 to 35 % higher in older people (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in older people were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for older people unless there is evidence of moderate or severe renal impairment (creatinine clearance below 60 ml /min) (see section 4.2).

Renal impairment
Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see section 4.2.

Hepatic impairment
In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of Tamiflu in its adopted therapeutic indications.

Teratology studies have been conducted in rats and rabbits at doses of up to 1,500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal development were observed. A rat fertility study up to a dose of 1,500 mg/kg/day demonstrated no adverse reactions on either sex. In pre- and post-natal rat studies, prolonged parturition was noted at 1,500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in 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 sensitisation to oseltamivir was observed in a "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active substance showed erythema after challenging the induced animals. Reversible irritancy of rabbits' eyes was detected.

Whereas very high oral single doses of oseltamivir phosphate salt, up to the highest dose tested (1,310 mg/kg), had no adverse reactions in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These reactions were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse reactions were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days post partum).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420),
Sodium dihydrogen citrate (E331[a])
Xanthan gum (E415)
Sodium benzoate (E211)
Saccharin sodium (E954)
Titanium dioxide (E171)
Tutti frutti flavour (including maltodextrins [maize], propylene glycol, arabic gum E414 and natural identical flavouring substances [mainly consisting of banana, pineapple and peach flavour]).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After reconstitution, store below 25 °C for 10 days.

6.4 Special precautions for storage

Do not store above 30°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

100 ml amber glass bottle (with child-resistant polypropylene screw cap, outer part: polyethylene; inner part: polypropylene; liner: polyethylene) with 13 g of powder for oral suspension, a plastic adapter (low density polyethylene) , plastic 3 ml oral dispenser (0.1 ml graduation) and 10 ml oral dispenser (0.5 ml graduation) (barrel and plunger: polypropylene, silicon based seal ring) and a plastic measuring cup (polypropylene).

Pack-size of one bottle.

6.6 Special precautions for disposal and other handling

It is recommended that Tamiflu oral suspension should be reconstituted by the pharmacist prior to being dispensed to the patient.

After reconstitution with 55 ml of water, the usable volume of oral suspension allows for the retrieval of a total of 10 doses of 30 mg oseltamivir.

<u>Preparation of oral suspension</u>
1. Tap the closed bottle gently several times to loosen the powder.
2. Measure 55 ml of water by filling the measuring cup to the indicated level (measuring cup included in the box).
3. Add all 55 ml of water into the bottle, recap the bottle and shake the closed bottle well for 15 seconds.
4. Remove the cap and push the bottle adapter into the neck of the bottle.
5. Close the bottle tightly with the cap (on the top of the bottle adapter). This will make sure that the bottle adapter fits in the bottle in the right position.

Tamiflu powder for suspension will appear as an opaque and white to light yellow suspension after reconstitution.

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 November 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 12 mg/ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of reconstituted suspension contains oseltamivir phosphate equivalent to 12 mg of oseltamivir.
One bottle of reconstituted suspension (75 ml) contains 900 mg of oseltamivir.

Excipients with known effect:
30 mg oseltamivir suspension delivers 0.9 g of sorbitol.
45 mg oseltamivir suspension delivers 1.3 g of sorbitol.
60 mg oseltamivir suspension delivers 1.7 g of sorbitol.
75 mg oseltamivir suspension delivers 2.1 g of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension
The powder is a granulate or clumped granulate with a white to light yellow colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of influenza
Tamiflu is indicated 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 two days of first onset of symptoms.

Prevention of influenza
- Post-exposure prevention in individuals 1 year of age or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

- The appropriate use of Tamiflu for prevention of influenza should be determined on a case by case basis by the circumstances and the population requiring protection. In exceptional situations (e.g. in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation) seasonal prevention could be considered in individuals one year of age or older.

- Tamiflu is indicated for post-exposure prevention of influenza in infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).

Tamiflu is not a substitute for influenza vaccination.

The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations (see section 5.1).

4.2 Posology and method of administration

Posology

Tamiflu suspension and Tamiflu hard capsules are bioequivalent formulations. 75 mg doses can be administered as either

- one 75 mg capsule or
- one 30 mg capsule plus one 45 mg capsule or
- by administering one 30 mg dose plus one 45 mg dose of suspension.

Adults, adolescents or children (> 40 kg) who are able to swallow capsules may receive appropriate doses of Tamiflu capsules.

For infants less than 1 year of age: This formulation is not suitable for dosing in infants less than 1 year age. For details, see sections below.

Treatment
Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

For adolescents (13 to 17 years of age) and adults: The recommended oral dose is 75 mg oseltamivir twice daily for 5 days.

Paediatric population

For infants and children 1 year of age or older: The recommended dose of Tamiflu oral suspension is indicated in the table below. Tamiflu 30 mg and 45 mg capsules are available as an alternative to the recommended dose of Tamiflu suspension.

The following weight-adjusted dosing regimens are recommended for infants and children 1 year of age or older:

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

Children weighing > 40 kg and who are able to swallow capsules may receive treatment with the adult dosage of 75 mg capsules twice daily for 5 days as an alternative to the recommended dose of Tamiflu suspension.

For infants less than 1 year of age: This formulation (Tamiflu 12 mg/ml powder for oral suspension) is unsuitable since the syringe provided in the pack (with mg markings) does not allow for appropriate dose adjustments and the use of syringes with ml markings may lead to unacceptable dosing inaccuracies. In the absence of the 6 mg/ml oral suspension formulation, the pharmacy compounded preparation should preferentially be used. Please refer to the SmPC for the 30 mg, 45 mg and 75 mg capsules (section 6.6).

Prevention
Post-exposure prevention
For adolescents (13 to 17 years of age) and adults: The recommended dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days. Therapy should begin as soon as possible within two days of exposure to an infected individual.

For infants and children1 year of age or older: Tamiflu 30 mg and 45 mg capsules are available as an alternative to the recommended dose of Tamiflu suspension.

The recommended post-exposure prevention dose of Tamiflu is:

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

Children weighing > 40 kg and who are able to swallow capsules may receive prophylaxis with a 75 mg capsule once daily for 10 days as an alternative to the recommended dose of Tamiflu suspension.

For infants less than 1 year of age: This formulation (Tamiflu 12 mg/ml powder for oral suspension) is unsuitable since the syringe provided in the pack (with mg markings) does not allow for appropriate dose adjustments and the use of syringes with ml markings may lead to unacceptable dosing inaccuracies. In the absence of a suitable formulation (6 mg/ml oral suspension), the pharmacy compounded preparation should preferentially be used. Please refer to the SmPC for the 30 mg. 45 mg and 75 mg capsules (section 4.2).

Prevention during an influenza epidemic in the community
Prevention during an influenza epidemic has not been studied in children below 12 years of age. The recommended dose for adults and adolescents for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to 6 weeks.

Special populations

Hepatic impairment
No dose adjustment is required either for treatment or for prevention in patients with hepatic dysfunction. No studies have been carried out in paediatric patients with hepatic disorder.

Renal impairment
Treatment of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment. Recommended doses are detailed in the table below.

Creatinine clearance	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) twice daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) once daily
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after each haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) single dose

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

Prevention of influenza: Dose adjustment is recommended for adults and adolescents (13 to 17 years of age) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for prevention
> 60 (ml/min)	75 mg once daily
> 30 to 60 (ml/min)	30 mg (suspension or capsules) once daily
> 10 to 30 (ml/min)	30 mg (suspension or capsules) every second day
≤ 10 (ml/min)	Not recommended (no data available)
Haemodialysis patients	30 mg after every second haemodialysis session
Peritoneal dialysis patients*	30 mg (suspension or capsules) once weekly

* Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher when automated peritoneal dialysis (APD) mode is used. Treatment mode can be switched from APD to CAPD if considered necessary by a nephrologist.

There is insufficient clinical data available in infants and children (12 years of age and younger) with renal impairment to be able to make any dosing recommendation.

Older people
No dose adjustment is required, unless there is evidence of moderate or severe renal impairment.

Immunocompromised patients
Longer duration of seasonal prophylaxis up to 12 weeks has been evaluated in immunocompromised patients (see sections 4.4, 4.8 and 5.1).

Method of administration
For dosing, an oral dispenser with 30 mg, 45 mg and 60 mg graduations is provided in the box. For accurate dosing, the oral dispenser supplied should be used exclusively (a syringe with ml markings cannot be used).
It is recommended that Tamiflu powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses (see section 5.1).

Tamiflu is not a substitute for influenza vaccination. Use of Tamiflu must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as Tamiflu is administered. Tamiflu should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community. Susceptibility of circulating influenza virus strains to oseltamivir has been shown to be highly variable (see section 5.1). Therefore, prescribers should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use Tamiflu.

Severe concomitant condition
No information is available regarding the safety and efficacy of oseltamivir in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalisation.

Immunocompromised patients
The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established (see section 5.1).

Cardiac / respiratory disease
Efficacy of oseltamivir in the treatment of subjects with chronic cardiac disease and/or respiratory disease has not been established. No difference in the incidence of complications was observed between the treatment and placebo groups in this population (see section 5.1).

Paediatric population
No data allowing a dose recommendation for premature children (<36 weeks post-conceptual age) are currently available.

Severe renal impairment
Dose adjustment is recommended for both treatment and prevention in adolescents (13 to 17 years or age) and adults with severe renal impairment. There is insufficient clinical data available in infants and children (1 year of age or older) with renal impairment to be able to make any dosing recommendation (see sections 4.2 and 5.2).

Neuropsychiatric events
Neuropsychiatric events have been reported during administration of Tamiflu in patients with influenza, especially in children and adolescents. These events are also experienced by patients with influenza without oseltamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8).

This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
Sorbitol can have a mild laxative effect.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see section 5.2), suggest that clinically significant drug interactions via these mechanisms are unlikely.

Probenecid
No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

Amoxicillin
Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated via the same pathway, suggesting that oseltamivir interaction with this pathway is weak.

Renal elimination
Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Additional information
No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir with paracetamol, acetylsalicylic acid, cimetidine, antacids

(magnesium and aluminium hydroxides and calcium carbonates), rimantadine or warfarin (in subjects stable on warfarin and without influenza).

4.6 Fertility, pregnancy and lactation

Pregnancy
While no controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, there is limited data available from post-marketing and retrospective observational surveillance reports. These data in conjunction with animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see section 5.3). Pregnant women may receive Tamiflu, after considering the available safety information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

Breastfeeding
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 subtherapeutic dose to the infant. Considering this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the breastfeeding woman, administration of oseltamivir may be considered, where there are clear potential benefits to breastfeeding mothers.

Fertility
Based on preclinical data, there is no evidence that Tamiflu has an effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Tamiflu is based on data from 6049 adult/adolescent and 1473 paediatric patients treated with Tamiflu or placebo for influenza, and on data from 3990 adult/adolescent and 253 paediatric patients receiving Tamiflu or placebo/no treatment for the prophylaxis of influenza in clinical trials. In addition, 475 immunocompromised patients (including 18 children, of these 10 Tamiflu and 8 placebo) received Tamiflu or placebo for the prophylaxis of influenza.

In adults/adolescents, the most commonly reported adverse reactions (ARs) were nausea and vomiting in the treatment studies, and nausea in the prevention studies. The majority of these ARs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. In children, the most commonly reported adverse reaction was vomiting. In the majority of patients, these ARs did not lead to discontinuation of Tamiflu.

The following serious adverse reactions have been rarely reported since oseltamivir has been marketed: Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders.
(Regarding neuropsychiatric disorders, see section 4.4.)

Tabulated list of adverse reactions
The ARs listed in the tables below fall into the following categories: 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*), and very rare (< *1/10,000*). ARs are added to the appropriate category in the tables according to the pooled analysis from clinical studies.

Treatment and prevention of influenza in adults and adolescents:
In adult/adolescent treatment and prevention studies, ARs that occurred the most frequently at the recommended dose (75 mg bid for 5 days for treatment and 75 mg od for up to 6 weeks for prophylaxis) are shown in Table 1.

The safety profile reported in subjects who 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, despite a longer duration of dosing in the prophylaxis studies.

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 arrhythmia	
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

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
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 prevention of influenza in children:

A total of 1473 children (including otherwise healthy children aged 1-12 years old and asthmatic children aged 6-12 years old) participated in clinical studies of oseltamivir given for the treatment of influenza. Of those, 851 children received treatment with oseltamivir suspension. A total of 158 children received the recommended dose of Tamiflu once daily in a post-exposure prophylaxis study in households (n = 99), a 6-week paediatric seasonal prophylaxis study (n = 49) and a 12-week paediatric seasonal prophylaxis study in immunocompromised subjects (n = 10).

Table 2 shows the most frequently reported ARs from paediatric clinical trials.

Table 2 Adverse reactions in studies investigating Tamiflu for treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg o.d.])

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Infections and infestations		Otitis media,		
Nervous system disorders		Headache		
Eye disorders:		Conjunctivitis (including red eyes, eye discharge and eye pain)		
Ear and labyrinth disorders:		Earache	Tympanic membrane disorder	
Respiratory, thoracic and mediastinal disorders	Cough, Nasal congestion	Rhinorrhoea		
Gastrointestinal disorders	Vomiting	Abdominal pain (incl. upper abdominal pain), Dyspepsia, Nausea		
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)	

Description of selected adverse reactions

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

In patients with influenza who were receiving Tamiflu, there have been postmarketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases resulting in self-injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. 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.

Hepato-biliary disorders
Hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.

Other special populations

Paediatric population (infants less than one year of age)
In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of oseltamivir therapy in 135 influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrohea and diaper rash being the most frequently reported

adverse events (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 oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies (comprising together more than 2,400 infants of that age class), epidemiological databases research and postmarketing reports suggest that the safety profile in infants less than one year of age is similar to the established safety profile of children aged one year and older.

Older people and patients with chronic cardiac and/or respiratory disease
The population included in the influenza treatment studies is comprised of otherwise healthy adults/adolescents and patients “at risk” (patients at higher risk of developing complications associated with influenza, e.g. older people 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.

Immunocompromised patients
In a 12-week prophylaxis study in 475 immunocompromised patients, including 18 children 1 to 12 years of age and older, the safety profile in the 238 patients who received oseltamivir was consistent with that previously observed in Tamiflu prophylaxis clinical studies.

Children with pre-existing bronchial asthma
In general, the adverse reaction profile in children with pre-existing bronchial asthma was qualitatively similar to that of otherwise healthy children.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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 4.8 Undesirable effects.

No specific antidote is known.

Paediatric population
Overdose has been reported more frequently for children than adults and adolescents. Caution should be exercised when preparing Tamiflu oral suspension and when administering Tamiflu products to children.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors ATC code: J05AH02

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into

uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity *in vivo* in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published studies.

Clinical studies

Treatment of influenza infection

The indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A.

Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population, which included both influenza-positive and -negative subjects (ITT), primary efficacy was reduced proportionally to the number of influenza-negative individuals. In the overall treatment population, influenza infection was confirmed in 67 % (range 46 % to 74 %) of the recruited patients. Of the older subjects, 64 % were influenza-positive and of those with chronic cardiac and/or respiratory disease 62 % were influenza-positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents 13 years of age and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever ≥ 37.8 °C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2,413) enrolled into treatment studies, oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95 % CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95 % CI 4.0 – 4.4 days; $p \leq 0.0001$).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1,063) in the placebo group to 8.6 % (116/1,350) in the oseltamivir treated population ($p = 0.0012$).

Treatment of influenza in high risk populations: The median duration of influenza illness in older subjects (≥ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In influenza-positive older people, oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics from 19 % (52/268) in the placebo group to 12 % (29/250) in the oseltamivir treated population ($p = 0.0156$).

In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17 % (22/133) in the placebo group and 14 % (16/118) in the oseltamivir treated population ($p = 0.5976$).

Treatment of influenza in children: In a study of otherwise healthy children (65 % influenza-positive) aged 1 to 12 years (mean age 5.3 years) who had fever (≥ 37.8 °C) plus either cough or coryza, 67 % of influenza-positive patients were infected with influenza A and 33 % with influenza B. Oseltamivir treatment, started within 48 hours of onset of symptoms, significantly reduced the time to freedom from illness (defined as the simultaneous return to normal health and activity and alleviation of fever,

cough and coryza) by 1.5 days (95 % CI 0.6 – 2.2 days; $p < 0.0001$) compared to placebo. Oseltamivir reduced the incidence of acute otitis media from 26.5 % (53/200) in the placebo group to 16 % (29/183) in the oseltamivir treated children ($p = 0.013$).

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) FEV_1 had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo ($p = 0.0148$) in this population.

The European Medicines Agency has deferred the obligation to submit the results of studies with Tamiflu in one or more subsets of the paediatric population in influenza. See section 4.2 for information on paediatric use.

The indication in infants below the age of 1 is based upon extrapolation of efficacy data from older children and the recommended posology is based upon pharmacokinetic modelling data (see Section 5.2).

Treatment of influenza B infection: Overall, 15 % of the influenza-positive population were infected by influenza B, proportions ranging from 1 to 33 % in individual studies. The median duration of illness in influenza B infected subjects did not differ significantly between the treatment groups in individual studies. Data from 504 influenza B infected subjects were pooled across all studies for analysis. Oseltamivir reduced the time to alleviation of all symptoms by 0.7 days (95 % CI 0.1 – 1.6 days; $p = 0.022$) and the duration of fever (≥ 37.8 °C), cough and coryza by one day (95 % CI 0.4 – 1.7 days; $p < 0.001$) compared to placebo.

Prevention of influenza
The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory-confirmed influenza. The virulence of influenza epidemics is not predictable and varies within a region and from season to season, therefore the number needed to treat (NNT) in order to prevent one case of influenza illness varies.

Post-exposure prevention: In a study in contacts (12.6 % vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily was started within 2 days of onset of symptoms in the index case and continued for seven days. Influenza was confirmed in 163 out of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12 %) in the placebo group to 2/205 (1 %) in the oseltamivir group (92 % reduction [95 % CI 6 – 16; $p \leq 0.0001$]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95 % CI 9 – 12) and was 16 (95 % CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and 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 the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20 % (27/136) in the group not receiving prevention to 7 % (10/135) in the group receiving prevention (62.7 % reduction [95 % CI 26.0 – 81.2; $p = 0.0042$]). In households of influenza-infected index cases, there was a reduction in the incidence of influenza from 26 % (23/89) in the group not receiving prevention to 11 % (9/84) in the group receiving prevention (58.5 % reduction [95 % CI 15.6 – 79.6; $p = 0.0114$]).
According to subgroup analysis in children at 1 to 12 years of age, the incidence of laboratory-confirmed clinical influenza among children was significantly reduced from 19 % (21/111) in the group not receiving prevention to 7 % (7/104) in the group receiving prevention (64.4 % reduction [95 % CI 15.8 – 85.0; $p = 0.0188$]). Among children who were not already shedding virus at baseline,

the incidence of laboratory-confirmed clinical influenza was reduced from 21 % (15/70) in the group not receiving prevention to 4 % (2/47) in the group receiving prevention (80.1 % reduction [95 % CI 22.0 – 94.9; p = 0.0206]). The NNT for the total paediatric population was 9 (95 % CI 7 – 24) and 8 (95 % CI 6, upper limit not estimable) in the whole population (ITT) and in paediatric contacts of infected index cases (ITTII), respectively.

Prevention during an influenza epidemic in the community: In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25/519 (4.8 %) in the placebo group to 6/520 (1.2 %) in the oseltamivir group (76 % reduction [95 % CI 1.6 – 5.7; p = 0.0006]) during a community outbreak of influenza. The NNT in this study was 28 (95 % CI 24 – 50).
A study in older people in nursing homes, where 80 % of participants received vaccine in the season of the study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4 %) in the placebo group to 1/276 (0.4 %) in the oseltamivir group (92 % reduction [95 % CI 1.5 – 6.6; p = 0.0015]). The NNT in this study was 25 (95 % CI 23 – 62).

Prophylaxis of influenza in immunocompromised patients: A double-blind, placebo-controlled, randomised study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised patients (388 patients with solid organ transplantation [195 placebo; 193 oseltamivir], 87 patients with haemopoetic stem cell transplantation [43 placebo; 44 oseltamivir], no patient with other immunosuppressant conditions), including 18 children 1 to 12 years of age. The primary endpoint in this study was the incidence of laboratory-confirmed clinical influenza as determined by viral culture and/or a four-fold rise in HAI antibodies. The incidence of laboratory-confirmed clinical influenza was 2.9 % (7/238) in the placebo group and 2.1 % (5/237) in the oseltamivir group (95 % CI -2.3 % – 4.1 %; p = 0.772).

Specific studies have not been conducted to assess the reduction in the risk of complications.

Oseltamivir 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. All patients who were found to carry oseltamivir-resistant virus did so transiently, cleared the virus normally and showed no clinical deterioration.

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	**Geno- and Phenotyping***
Adults and adolescents	4/1,245 (0.32 %)	5/1,245 (0.4 %)
Children (1-12 years)	19/464 (4.1 %)	25/464 (5.4 %)

* Full genotyping was not performed in all studies.

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. Resistant strains selected during oseltamivir treatment have been isolated from both immunocompetent and immunocompromised patients. Immunocompromised patients and young children are at a higher risk of developing oseltamivir-resistant virus during treatment.

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. Since 2007 resistance associated H275Y mutation in seasonal H1N1 strains has become widespread. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. In 2008,

H275Y was found in > 99 % of circulating H1N1 influenza isolates in Europe. The 2009 H1N1 influenza ("swine flu") was almost uniformly susceptible to oseltamivir, with only sporadic reports of resistance in connection with both therapeutic and prophylactic regimens.

5.2 Pharmacokinetic properties

General Information

Absorption
Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5 % relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution
The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate distributes to all sites of influenza virus spread.

The binding of the oseltamivir carboxylate to human plasma protein is negligible (approximately 3 %).

Biotransformation
Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In vitro* studies demonstrated that neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination
Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 l/h) exceeds glomerular filtration rate (7.5 l/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Other special populations

Paediatric population
Infants less than 1 year of age: The pharmacokinetics, pharmacodynamics and safety of Tamiflu have been evaluated in two uncontrolled open-label studies including influenza infected children less than one year of age (n=135). 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 infants 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 (see sections 4.1 and 4.2).The reported adverse events were consistent with the established safety profile in older children.

There are no data available for infants below 1 year of age for post exposure prevention of influenza. Prevention during an influenza epidemic in the community has not been studied in children below 12 years of age.

Infants and children 1 year of age or older: The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in infants, children and adolescents 1 to 16 years of age. Multiple-dose pharmacokinetics were studied in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the pro-drug and its active metabolite faster than adults,

resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older are similar to those in adults.

Older people
Exposure to the active metabolite at steady state was 25 to 35 % higher in older people (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in older people were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for older people unless there is evidence of moderate or severe renal impairment (creatinine clearance below 60 ml /min) (see section 4.2).

Renal impairment
Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see section 4.2.

Hepatic impairment
In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of Tamiflu in its adopted therapeutic indications.

Teratology studies have been conducted in rats and rabbits at doses of up to 1,500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal development were observed. A rat fertility study up to a dose of 1,500 mg/kg/day demonstrated no adverse reactions on either sex. In pre- and post-natal rat studies, prolonged parturition was noted at 1,500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in 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 sensitisation to oseltamivir was observed in a "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active substance showed erythema after challenging the induced animals. Reversible irritancy of rabbits' eyes was detected.

Whereas very high oral single doses of oseltamivir phosphate salt, up to the highest dose tested (1,310 mg/kg), had no adverse reactions in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These reactions were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse reactions were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days post partum).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420),
Sodium dihydrogen citrate (E331[a])
Xanthan gum (E415)
Sodium benzoate (E211)
Saccharin sodium (E954)
Titanium dioxide (E171)
Tutti frutti flavour (including maltodextrins [maize], propylene glycol, arabic gum E414 and natural identical flavouring substances [mainly consisting of banana, pineapple and peach flavour]).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After reconstitution, store below 25 °C for 10 days or in a refrigerator (2 °C – 8 °C) for 17 days.

6.4 Special precautions for storage

Do not store above 30°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

100 ml amber glass bottle (with child-resistant polypropylene screw cap, outer part: polyethylene; inner part: polypropylene; liner: polyethylene) with 30 g of powder for oral suspension, a plastic adapter (low density polyethylene), a plastic oral dispenser (30 mg, 45 mg and 60 mg graduation) (barrel and plunger: polypropylene; silicon based seal ring) and a plastic measuring cup (polypropylene).

Pack-size of one bottle.

6.6 Special precautions for disposal and other handling

It is recommended that Tamiflu oral suspension should be reconstituted by the pharmacist prior to being dispensed to the patient.

After reconstitution with 52 ml of water, the usable volume of oral suspension allows for the retrieval of a total of 10 doses of 75 mg oseltamivir.

Only the syringe included in the package with doses indicated in mg should be used. It cannot be replaced by a syringe with ml markings.

<u>Preparation of oral suspension</u>

1. Tap the closed bottle gently several times to loosen the powder.
2. Measure 52 ml of water by filling the measuring cup to the indicated level (measuring cup included in the box).
3. Add all 52 ml of water into the bottle, recap the bottle and shake the closed bottle well for 15 seconds.
4. Remove the cap and push the bottle adapter into the neck of the bottle.

5. Close the bottle tightly with the cap (on the top of the bottle adapter). This will make sure that the bottle adapter fits in the bottle in the right position.

Tamiflu powder for suspension will appear as an opaque and white to light yellow suspension after reconstitution.

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2002
Date of last renewal: 20 June 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Str. 1
D- 79639 Grenzach –Wyhlen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

- **Conditions or Restrictions with Regard to the Safe and Effective Use of the Medicinal Product**

The MAH shall ensure that at the launch of Tamiflu 6 mg/ml powder for oral suspension, all physicians who are expected to prescribe or use Tamiflu are provided with a Direct Healthcare Professional Communication letter, the text of which is appended to the CHMP assessment report. The MAH shall agree the communication plan for the DHPC letter with the National Competent Authority in the Member States where the letter will be distributed.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 30 mg hard capsules
Oseltamivir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains oseltamivir phosphate equivalent to 30 mg of oseltamivir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tamiflu 30 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 30 mg capsules
Oseltamivir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 45 mg hard capsules
Oseltamivir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains oseltamivir phosphate equivalent to 45 mg of oseltamivir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/004

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tamiflu 45 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 45 mg capsules
Oseltamivir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 75 mg hard capsules
Oseltamivir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains oseltamivir phosphate equivalent to 75 mg of oseltamivir.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tamiflu 75 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 75 mg capsules
Oseltamivir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 6 mg/ml powder for oral suspension
Oseltamivir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 bottle contains 390 mg of oseltamivir. Final volume of the bottle after reconstitution is 65 ml. Each ml of suspension contains 6 mg oseltamivir.

3. LIST OF EXCIPIENTS

Also contains sorbitol.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 bottle
Also contains 1 plastic bottle adapter, 1 plastic measuring cup (55 ml), 1 plastic 3 ml oral dispenser and 1 plastic 10 ml oral dispenser.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oral use after reconstitution
Shake bottle well before use
Caution: dispenser graduated in millilitre (ml)

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Powder: Do not store above 30°C
After reconstitution, store below 25 °C for 10 days

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/005

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tamiflu

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for bottle

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 6 mg/ml powder for oral suspension
Oseltamivir

2. METHOD OF ADMINISTRATION

For oral use after reconstitution
Shake bottle well before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

The volume of the reconstituted suspension is 65 ml
1 ml contains 6 mg oseltamivir

6. OTHER

Powder: Do not store above 30 ºC
Oral suspension: Store below 25 °C for 10 days

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 12 mg/ml powder for oral suspension
Oseltamivir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 bottle contains 900 mg of oseltamivir. Final volume of the bottle after reconstitution is 75 ml. Each ml of suspension contains 12 mg oseltamivir.

3. LIST OF EXCIPIENTS

Also contains sorbitol.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 bottle
Also contains 1 plastic bottle adapter, 1 plastic measuring cup (52 ml) and 1 plastic oral dispenser

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For oral use after reconstitution
Shake bottle well before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Powder: Do not store above 30°C
After reconstitution, store below 25 °C for 10 days or in a refrigerator (2 °C - 8 °C) for 17 days

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/222/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tamiflu

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label for bottle

1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 12 mg/ml powder for oral suspension
Oseltamivir

2. METHOD OF ADMINISTRATION

Read the package leaflet before use
For oral use after reconstitution
Shake bottle well before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

The volume of the reconstituted suspension is 75 ml
1 ml contains 12 mg oseltamivir

6. OTHER

Also contains sorbitol.
Powder: Do not store above 30 ºC
Oral suspension: Store below 25 °C for 10 days or in a refrigerator (2 °C - 8 °C) for 17 days

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Tamiflu 30 mg hard capsules
oseltamivir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. **What Tamiflu is and what it is used for**
2. **What you need to know before you take Tamiflu**
3. **How to take Tamiflu**
4. **Possible side effects**
5. **How to store Tamiflu**
6. **Contents of the pack and other information**

1. What Tamiflu is and what it is used for

- Tamiflu is used for adults, adolescents, children and infants (including full-term newborn babies) for **treating flu** (*influenza*). It can be used when you have flu symptoms, and the flu virus is known to be going round in your community.
- Tamiflu can also be prescribed for adults, adolescents, children and infants above 1 year of age for **preventing flu,** on a case-by-case basis – for instance, if you have been in contact with someone who has flu.
- Tamiflu may be prescribed for adults, adolescents, children and infant (including full-term newborn babies) as **preventive treatment** in exceptional circumstances – for example, if there is a global epidemic of flu (a flu *pandemic*) and the seasonal flu vaccine may not provide sufficient protection.

Tamiflu contains *oseltamivir*, which belongs to a group of medicines named *neuraminidase inhibitors*. These medicines prevent the flu virus from spreading inside the body. They help to ease or prevent the symptoms of the flu virus infection.

Influenza, usually called flu, is an infection caused by a virus. The signs of flu often include a sudden fever (more than 37.8 °C), cough, runny or stuffy nose, headaches, muscle aches and extreme tiredness. These symptoms can also be caused by other infections. True influenza infection only occurs during annual outbreaks (*epidemics*) when flu viruses are spreading in the local community. Outside epidemic periods, flu-like symptoms are usually caused by a different type of illness.

2. What you need to know before you take Tamiflu

Do not take Tamiflu:
- **if you are allergic** (*hypersensitive*) to oseltamivir or any of the other ingredients of Tamiflu listed in section 6**.**

Talk to your doctor if this applies to you. **Do not take Tamiflu.**

Warnings and precautions:
Before you take Tamiflu, make sure the prescribing doctor knows
- if you are **allergic to other medicines**
- if you have **problems with your kidneys**. If so, your dose may need adjustment
- if you have a **severe medical condition**, which may require immediate hospitalisation
- if your **immune system** is not working
- if you have chronic **heart disease** or **respiratory disease**.

During treatment with Tamiflu, **tell a doctor immediately**:
- if you notice changes in behaviour or mood (*neuropsychiatric events*), especially in children and adolescents). These may be signs of rare but serious side effects.

Tamiflu is not a flu vaccine
Tamiflu is not a vaccine: it treats infection, or prevents the flu virus spreading. A vaccine gives you antibodies against the virus. Tamiflu will not change the effectiveness of a flu vaccine, and you might be prescribed both by your doctor.

Other medicines and Tamiflu
Tell your doctor or pharmacist if you are taking any other medicines, or have recently taken any. This includes medicines obtained without a prescription. The following medicines are particularly important:
- chlorpropamide (used to treat diabetes)
- methotrexate (used to treat e.g. rheumatoid arthritis)
- phenylbutazone (used to treat pain and inflammation)
- probenecid (used to treat gout)

Pregnancy and breast-feeding
You must tell your doctor if you are pregnant, if you think you are pregnant or if you are trying to get pregnant so that your doctor can decide if Tamiflu is right for you.

The effects on breast-fed infants are unknown. You must tell your doctor if you are breast-feeding so that your doctor can decide if Tamiflu is right for you.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Tamiflu has no effect on your ability to drive or use machines.

3. How to take Tamiflu

Take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Take Tamiflu as soon as possible, ideally within two days of the flu symptoms starting.

The recommended doses

For treating flu, take two doses daily. It is usually convenient to take one dose in the morning and one in the evening. **It is important to complete the whole 5-day course**, even if you start to feel better quickly.

For preventing flu or after being exposed to an infected person, take one dose daily for 10 days. It is best to take this in the mornings with breakfast.

In special situations, such as widespread flu or for patients with a weak immune system, treatment will continue for up to 6 or 12 weeks.

The recommended dose is based on the patient's body weight. You must use the amount of oral capsules or suspension prescribed by the doctor.

Adults, and adolescents 13 years and over

Body weight	**Treating flu:** dose *for 5 days*	**Preventing flu:** dose *for 10 days*
40 kg or more	75 mg twice daily	75 mg once daily

75 mg can be made up of a 30 mg capsule plus a 45 mg capsule

Children 1 to 12 years

Body weight	**Treating flu:** dose *for 5 days*	**Preventing flu:** dose *for 10 days*
10 to 15 kg	30 mg twice daily	30 mg once daily
More than 15 kg and up to 23 kg	45 mg twice daily	45 mg once daily
More than 23 kg and up to 40 kg	60 mg twice daily	60 mg once daily
More than 40 kg	75 mg twice daily	75 mg once daily

75 mg can be made up of a 30 mg capsule plus a 45 mg capsule

Infants less than 1 year (0 to 12 months)
Giving Tamiflu to infants less than 1 year old for preventing flu during flu pandemic should be based upon the judgment of a doctor after considering the potential benefit versus any potential risk to the infant.

Body weight	**Treating flu:** dose *for 5 days*	**Preventing flu:** dose *for 10 days*
3 kg to 10+ kg,	3 mg per kg body weight, twice daily	3 mg per kg, once daily

mg per kg = *mg for each kilogram of the infant's body weight. For example:*
If a 6-month-old weighs 8 kg, the dose is
8 kg x 3mg per kg = 24 mg

Method of administration
Swallow the capsules whole with water. Do not break or chew the capsules.

Tamiflu can be taken with or without food, although taking it with food can reduce the chance of feeling or being sick (nausea or vomiting).

People who find it hard to take capsules can use a liquid medicine, *Tamiflu oral suspension.* If you need Tamiflu oral suspension, but it's not available from your pharmacy, you can make a liquid form of Tamiflu from these capsules. **See *Making liquid Tamiflu at home,*** over the page.

If you take more Tamiflu than you should
Stop taking Tamiflu and contact a doctor or pharmacist immediately.
In most cases of overdose, people have not reported any side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.
Overdose has been reported to have occurred more frequently when Tamiflu was given to children than to adults and adolescents. Caution should be exercised when preparing liquid Tamiflu for children and when administering Tamiflu capsules or liquid Tamiflu to children.

If you forget to take Tamiflu
Do not take a double dose to make up for a forgotten capsule.

If you stop taking Tamiflu
There are no side effects when you stop Tamiflu. But if Tamiflu is stopped earlier than your doctor told you, the symptoms of flu may come back. Always complete the course that your doctor prescribed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Many of the side effects listed below may also be caused by influenza.

The following serious side effects have been rarely reported since oseltamivir has been marketed:

- Anaphylactic and anaphylactoid reactions: severe allergic reactions, with face and skin swelling, itchy rashes, low blood pressure and breathing difficulties
- Hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice): yellowing of the skin and white of the eyes, change in stool color, changes in behaviour
- Angioneurotic oedema: sudden onset of severe swelling of the skin mainly around the head and neck area, including eyes and tongue, with difficulties breathing
- Stevens-Johnson syndrome and toxic epidermal necrolysis: complicated, possibly life-threatening allergic reaction, severe inflammation of the outer and possibly inner skin, initially with fever, sore throat, and fatigue, skin rashes, leading to blisters, peeling, shedding of larger areas of skin, possible breathing difficulties and low blood pressure
- Gastrointestinal bleeding: prolonged bleeding from the large bowel or spitting up blood
- Neuropsychiatric disorders, as described below.

If you notice any of these symptoms, **get medical help immediately.**

The most frequently (very common and common) reported side effects of Tamiflu are feeling or being sick (nausea, vomiting), stomach ache, stomach upset, headache and pain. These side effects mostly occur after the first dose of the medicine and will usually stop as treatment continues. The frequency of these effects is reduced if the medicinal product is taken with food.

Rare but serious effects: get medical help at once
(*These may affect up to 1 in 1,000 people*)
During Tamiflu treatment, rare events have been reported that include

- Convulsions and delirium, including altered level of consciousness
- Confusion, abnormal behaviour
- Delusions, hallucinations, agitation, anxiety, nightmares

These are reported primarily among children and adolescents and often started suddenly and resolved rapidly. A few cases resulted in self-injury, some with fatal outcome. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Tamiflu.

- Patients, especially children and adolescents, should be closely monitored for the behavioural changes described above.

If you notice any of these symptoms, especially in younger people, **get medical help immediately.**

Adults and adolescents 13 and over

Very common side effects
(may affect more than 1 in 10 people)

- Headache
- Nausea.

Common side effects
(may affect up to 1 in 10 people)

- Bronchitis
- Cold sore virus
- Cough
- Dizziness
- Fever
- Pain
- Pain in limb
- Runny nose
- Sleeping difficulties
- Sore throat
- Stomach ache
- Tiredness
- Upper abdominal fullness
- Upper respiratory tract infections (inflammation of the nose, throat and sinuses)
- Upset stomach
- Vomiting.

Uncommon side effects
(may affect up to 1 in 100 people)

- Allergic reactions
- Altered level of consciousness
- Convulsion
- Heart rhythm abnormalities
- Mild to severe liver function disorders
- Skin reactions (inflammation of the skin, red and itchy rash, scaling skin).

Rare side effects
(may affect up to 1 in 1,000 people)

- Thrombocytopenia (low platelet count)
- Visual disturbances.

Children 1 to 12 years

Very common side effects
(may affect more than 1 in 10 people)

- Cough
- Nasal congestion
- Vomiting.

Common side effects
(may affect up to 1 in 10 people)

- Conjunctivitis (red eyes and discharge or pain in the eye)
- Ear inflammation and other ear disorders
- Headache
- Nausea
- Runny nose
- Stomach ache
- Upper abdominal fullness
- Upset stomach.

Uncommon side effects
(may affect up to 1 in 100 people)
- Inflammation of the skin
- Tympanic membrane (eardrum) disorder.

Infants less than 1 year
The reported side effects in infants 0 to 12 months old are mostly similar to the side effects reported for older children (1 year old or older). Additionally, diarrhoea and diaper rash have been reported..

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist. However,
- **if you or your child are repeatedly sick,** or
- **if the influenza symptoms get worse or the fever continues**

Tell your doctor as soon as possible.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tamiflu

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25 °C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Tamiflu contains
- Each hard capsule contains oseltamivir equivalent to 30 mg of oseltamivir
- The other ingredients are:
  capsule contents: pregelatinised starch, talc, povidone, croscarmellose sodium and sodium stearyl fumarate
  capsule shell: gelatin, yellow iron oxide (E172), red iron oxide (E172) and titanium dioxide (E171)
  printing ink: shellac (E904), titanium dioxide (E171) and FD and C Blue 2 (indigo carmine E132).

What Tamiflu looks like and contents of the pack
The 30 mg hard capsule consists of a light yellow opaque body bearing the imprint “ROCHE” and a light yellow opaque cap bearing the imprint “30 mg”. Imprints are blue.

Tamiflu 30 mg hard capsules are available in blister packs of 10.

Marketing Authorisation Holder and Manufacturer

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

Roche Pharma AG
Emil-Barell-Str. 1,
D-79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
N.V. Roche S.A.
Tél/Tel: +32 (0) 2 525 82 11

България
Рош България ЕООД
Тел: +359 2 818 44 44

Česká republika
Roche s. r. o.
Tel: +420 - 2 20382111

Danmark
Roche a/s
Tlf: +45 - 36 39 99 99

Deutschland
Roche Pharma AG
Tel: +49 (0) 7624 140

Eesti
Roche Eesti OÜ
Tel: + 372 - 6 177 380

Ελλάδα
Roche (Hellas) A.E.
Τηλ: +30 210 61 66 100

España
Roche Farma S.A.
Tel: +34 - 91 324 81 00

France
Roche
Tél: +33 (0) 1 47 61 40 00

Hrvatska
Roche d.o.o
Tel: +385 1 4722 333

Lietuva
UAB “Roche Lietuva”
Tel: +370 5 2546799

Luxembourg/Luxemburg
(Voir/siehe Belgique/Belgien)

Magyarország
Roche (Magyarország) Kft.
Tel: +36 - 23 446 800

Malta
(ara Renju Unit)

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438050

Norge
Roche Norge AS
Tlf: +47 - 22 78 90 00

Österreich
Roche Austria GmbH
Tel: +43 (0) 1 27739

Polska
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

Portugal
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

România
Roche România S.R.L.
Tel: +40 21 206 47 01

Ireland
Roche Products (Ireland) Ltd.
Tel: +353 (0) 1 469 0700

Ísland
Roche a/s
c/o Icepharma hf
Sími: +354 540 8000

Italia
Roche S.p.A.
Tel: +39 - 039 2471

Κύπρος
Γ.Α.Σταμάτης & Σια Λτδ.
Τηλ: +357 - 22 76 62 76

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

Slovenija
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

United Kingdom
Roche Products Ltd.
Tel: +44 (0) 1707 366000

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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Information for the user

For people who find it hard to take capsules, including very young children, there's a liquid medicine, *Tamiflu oral suspension*.

If you need a liquid medicine, but it's not available, a suspension can be made up at the pharmacy from Tamiflu capsules (see *Information for healthcare professionals).* This pharmacy preparation is the preferred option.

If the pharmacy preparation is not available either, you can make liquid Tamiflu from these capsules at home.

The dose is the same for treating or preventing flu. The difference is how often it is given.

Making liquid Tamiflu at home

- **If you have the right capsule** for the dose needed (a 30 mg or a 60 mg dose), you will open the capsule and stir its contents into one teaspoon (or less) of a suitable sweetened food product. This is usually suitable for children over 1 year. **See the upper set of instructions**.

- **If you need smaller doses,** making liquid Tamiflu from capsules involves extra steps. This is suitable for younger children and babies: they usually need a Tamiflu dose of less than 30 mg. **See the lower set of instructions**.

Children 1 to 12 years

To make a 30 mg or a 60 mg dose,
you need:

- **One or two 30 mg Tamiflu capsule(s)**
- **Sharp scissors**
- **One small bowl**
- **Teaspoon (5 ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of the powder.
  Examples are: chocolate or cherry syrup, and dessert toppings such as caramel or fudge sauce. Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Check the dose is correct

To find the correct amount to use, find the patient's weight on the left of the table.
Look at the right column to check the number of capsules you will need to give the patient for a single dose. The amount is the same whether treating or preventing flu.

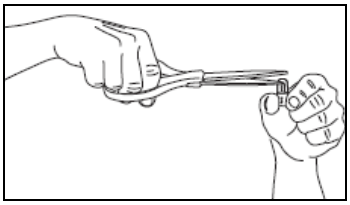
30 mg dose	
60 mg dose	

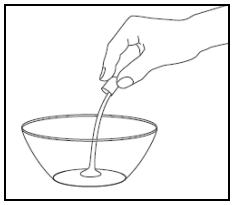
You should use only 30 mg capsules for 30 mg and 60 mg doses. Do not try to make a 45 mg or 75 mg dose by using the contents of 30 mg capsules. Use the appropriate size capsule instead.

Weight	**Dose of Tamiflu**	**Number of capsules**
Up to 15 kg	30 mg	1 capsule
~~15 kg up to 23 kg~~	~~45 mg~~	**Do not use 30 mg capsules**
23 kg up to 40 kg	60 mg	2 capsules

Step 2: Pour all the powder into a bowl

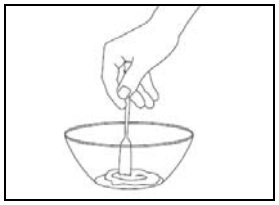
Hold a **30 mg capsule** upright over a bowl and carefully snip off the rounded tip with scissors.
Pour all of the powder into the bowl.
Open a second capsule for a 60 mg dose. Pour all of the powder into the bowl.
Be careful with the powder, because it may irritate your skin and eyes.





Step 3: Sweeten the powder and give the dose

Add a small amount – no more than one teaspoonful – of sweet food to the powder in the bowl.
This is to hide the bitter taste of the Tamiflu powder.
Stir the mixture well.



Give the whole contents of the bowl to the patient straight away.

If there is some mixture left in the bowl, rinse the bowl with a small amount of water and get the patient to drink it all.

Repeat this procedure every time you need to give the medicine.

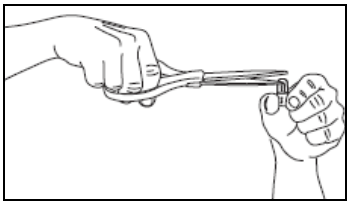
Infants less than 1 year

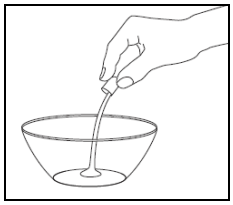
To make a smaller single dose, you need:

- **One 30 mg Tamiflu capsule**
- **Sharp scissors**
- **Two small bowls** (use separate pairs of bowls for each child)
- **One large oral dose dispenser** to measure out water – a 5 or 10 ml dispenser
- **One small oral dose dispenser** showing measurements of 0.1 ml, to give the dose
- **Teaspoon (5 ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of the Tamiflu.
  Examples are: chocolate or cherry syrup and dessert toppings such as caramel or fudge sauce.
  Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Pour all the powder into a bowl

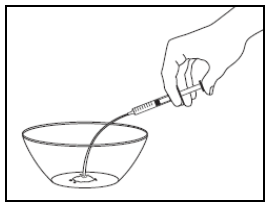
Hold a **30 mg capsule** upright over one of the bowls and carefully snip off the rounded tip with scissors. Be careful with the powder: it may irritate your skin and eyes.
Pour all of the powder into the bowl, whatever the dose you are making.
The amount is the same whether you are treating or preventing flu.





Step 2: Add water to dilute the medicine

Use the larger dispenser to draw up **5 ml water.**



Add the water to the powder in the bowl.

Stir the mixture with the teaspoon for about 2 minutes.

Don’t worry if not all of the powder dissolves. The undissolved powder is just inactive ingredients.

Step 3: Choose the correct amount for your child’s weight

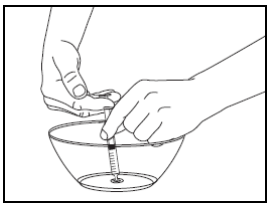
Look up the child’s weight on the left side of the table.
The column on the right of the table shows how much of the liquid mixture you will need to draw up.

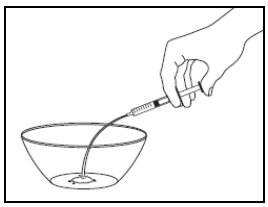
Infants less than 1 year (including full-term newborn babies)

Child's weight (nearest)	**How much mixture to draw up**
3 kg	1.5 ml
3.5 kg	1.8 ml
4 kg	2.0 ml
4.5 kg	2.3 ml
5 kg	2.5 ml
5.5 kg	2.8 ml
6 kg	3.0 ml
6.5 kg	3.3 ml
7 kg	3.5 ml
7.5 kg	3.8 ml
8 kg	4.0 ml
8.5 kg	4.3 ml
9 kg	4.5 ml
9.5 kg	4.8 ml
10 kg or more	5.0 ml

Step 4: Draw up the liquid mixture

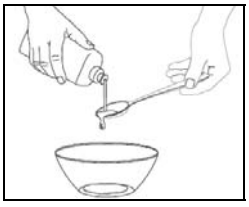
Make sure you have the right size dispenser.
Draw up the correct amount of liquid mixture from the first bowl.
Draw it up carefully so as not to include air bubbles.
Gently squirt the correct dose into the second bowl.

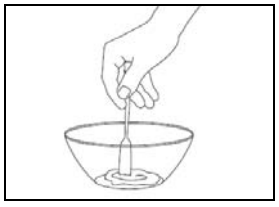




Step 5: Sweeten and give to the child

Add a small amount – no more than one teaspoonful – of a sweet food to the second bowl.
This is to hide the bitter taste of the Tamiflu.
Mix the sweet food and Tamiflu liquid well.





Give the whole contents of the second bowl (Tamiflu liquid mixture with sweet food added) to the child straight away.

If there is anything left in the second bowl, rinse the bowl with a small amount of water and get the child to drink it all. For children unable to drink from a bowl, spoon-feed or use a bottle to feed the child the remaining liquid.

Give the child something to drink.

Throw away any unused liquid left in the first bowl.

Repeat this procedure every time you need to give the medicine.

Information for healthcare professionals only

Patients who are unable to swallow capsules:
Commercially manufactured Tamiflu for oral suspension (6mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. In the event thatTamiflu powder for oral suspension is not available, the pharmacist may compound a suspension (6 mg/ml) from Tamiflu capsules. If the pharmacy compounded suspension is also not available, patients may prepare the suspension from capsules at home.

Oral dose dispensers (oral syringes) of appropriate volume and grading should be provided for administering the pharmacy compounded suspension, and for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the dispensers. For home preparation, separate dispensers should be provided for taking the correct volume of water and for measuring the Tamiflu-water mixture. For measuring 5.0 ml of water, dispensers of 5 ml or 10 ml should be used.

The appropriate dispenser sizes for taking the correct volume of Tamiflu suspension (6 mg/ml) are shown below.

Infants less than 1 year (including full term new born babies):

Dose of Tamiflu	**Amount of Tamiflu suspension**	**Dispenser size to use (grading 0.1 ml)**
9 mg	1.5 ml	2.0 ml (or 3.0 ml)
10 mg	1.7 ml	2.0 ml (or 3.0 ml)
11.25 mg	1.9 ml	2.0 ml (or 3.0 ml)
12.5 mg	2.1 ml	3.0 ml
13.75 mg	2.3 ml	3.0 ml
15 mg	2.5 ml	3.0 ml
16.25 mg	2.7 ml	3.0 ml
18 mg	3.0 ml	3.0 ml (or 5.0 ml)
19.5 mg	3.3 ml	5.0 ml
21 mg	3.5 ml	5.0 ml
22.5 mg	3.8 ml	5.0 ml
24 mg	4.0 ml	5.0 ml
25.5 mg	4.3 ml	5.0 ml
27 mg	4.5 ml	5.0 ml
28.5 mg	4.8 ml	5.0 ml
30 mg	5.0 ml	5.0 ml

Package Leaflet: Information for the user

Tamiflu 45 mg hard capsules
oseltamivir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. **What Tamiflu is and what it is used for**
2. **What you need to know before you take Tamiflu**
3. **How to take Tamiflu**
4. **Possible side effects**
5. **How to store Tamiflu**
6. **Contents of the pack and other information**

1. What Tamiflu is and what it is used for

- Tamiflu is used for adults, adolescents, children and infants (including full-term newborn babies) for **treating flu** (*influenza*). It can be used when you have flu symptoms, and the flu virus is known to be going round in your community.
- Tamiflu can also be prescribed for adults, adolescents, children and infants above 1 year of age for **preventing flu,** on a case-by-case basis – for instance, if you have been in contact with someone who has flu.
- Tamiflu may be prescribed for adults, adolescents, children and infants (including full-term newborn babies) as **preventive treatment** in exceptional circumstances – for example, if there is a global epidemic of flu (a flu *pandemic*) and the seasonal flu vaccine may not provide sufficient protection.

Tamiflu contains *oseltamivir*, which belongs to a group of medicines named *neuraminidase inhibitors*. These medicines prevent the flu virus from spreading inside the body. They help to ease or prevent the symptoms of the flu virus infection.

Influenza, usually called flu, is an infection caused by a virus. The signs of flu often include a sudden fever (more than 37.8 °C), cough, runny or stuffy nose, headaches, muscle aches and extreme tiredness. These symptoms can also be caused by other infections. True influenza infection only occurs during annual outbreaks (*epidemics*) when flu viruses are spreading in the local community. Outside epidemic periods, flu-like symptoms are usually caused by a different type of illness.

2. What you need to know before you take Tamiflu

Do not take Tamiflu:
- **if you are allergic** (*hypersensitive*) to oseltamivir or any of the other ingredients of Tamiflu listed in section 6**.**

Talk to your doctor if this applies to you. **Do not take Tamiflu.**

Warnings and precautions:
Before you take Tamiflu, make sure the prescribing doctor knows
- if you are **allergic to other medicines**
- if you have **problems with your kidneys**. If so, your dose may need adjustment
- if you have a **severe medical condition**, which may require immediate hospitalisation
- if your **immune system** is not working
- if you have chronic **heart disease** or **respiratory disease**.

During treatment with Tamiflu, **tell a doctor immediately**:
- if you notice changes in behaviour or mood (*neuropsychiatric events*), especially in children and adolescents). These may be signs of rare but serious side effects.

Tamiflu is not a flu vaccine
Tamiflu is not a vaccine: it treats infection, or prevents the flu virus spreading. A vaccine gives you antibodies against the virus. Tamiflu will not change the effectiveness of a flu vaccine, and you might be prescribed both by your doctor.

Other medicines and Tamiflu
Tell your doctor or pharmacist if you are taking any other medicines, or have recently taken any. This includes medicines obtained without a prescription. The following medicines are particularly important:
- chlorpropamide (used to treat diabetes)
- methotrexate (used to treat e.g. rheumatoid arthritis)
- phenylbutazone (used to treat pain and inflammation)
- probenecid (used to treat gout)

Pregnancy and breast-feeding
You must tell your doctor if you are pregnant, if you think you are pregnant or if you are trying to get pregnant so that your doctor can decide if Tamiflu is right for you.

The effects on breast-fed infants are unknown. You must tell your doctor if you are breast-feeding so that your doctor can decide if Tamiflu is right for you.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Tamiflu has no effect on your ability to drive or use machines.

3. How to take Tamiflu

Take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Take Tamiflu as soon as possible, ideally within two days of the flu symptoms starting.

The recommended doses

For treating flu, take two doses daily. It is usually convenient to take one dose in the morning and one in the evening. **It is important to complete the whole 5-day course**, even if you start to feel better quickly.

For preventing flu or after being exposed to an infected person, take one dose daily for 10 days. It is best to take this in the mornings with breakfast.

In special situations, such as widespread flu or for patients with a weak immune system, treatment will continue for up to 6 or 12 weeks.

The recommended dose is based on the patient's body weight. You must use the amount of oral capsules or suspension prescribed by the doctor.

Adults, and adolescents 13 years and over

Body weight	**Treating flu:** dose *for 5 days*	**Preventing flu:** dose *for 10 days*
40 kg or more	75 mg twice daily	75 mg once daily

75 mg can be made up of a 30 mg capsule plus a 45 mg capsule

Children 1 to 12 years

Body weight	**Treating flu:** dose *for 5 days*	**Preventing flu:** dose *for 10 days*
10 to 15 kg	30 mg twice daily	30 mg once daily
More than 15 kg and up to 23 kg	45 mg twice daily	45 mg once daily
More than 23 kg and up to 40 kg	60 mg twice daily	60 mg once daily
More than 40 kg	75 mg twice daily	75 mg once daily

75 mg can be made up of a 30 mg capsule plus a 45 mg capsule

Infants less than 1 year (0 to 12 months)
Giving Tamiflu to infants less than 1 year old for preventing flu during flu pandemic should be based upon the judgment of a doctor after considering the potential benefit versus any potential risk to the infant.

Body weight	**Treating flu:** dose *for 5 days*	**Preventing flu:** dose *for 10 days*
3 kg to 10+ kg,	3 mg per kg body weight, twice daily	3 mg per kg, once daily

mg per kg = *mg for each kilogram of the infant's body weight. For example:*
If a 6-month-old weighs 8 kg, the dose is
8 kg x 3mg per kg = 24 mg

Method of administration
Swallow the capsules whole with water. Do not break or chew the capsules.

Tamiflu can be taken with or without food, although taking it with food can reduce the chance of feeling or being sick (nausea or vomiting).

People who find it hard to take capsules can use a liquid medicine, *Tamiflu oral suspension*. If you need Tamiflu oral suspension, but it's not available from your pharmacy, you can make a liquid form of Tamiflu from these capsules. **See *Making liquid Tamiflu at home,*** over the page.

If you take more Tamiflu than you should
Stop taking Tamiflu and contact a doctor or pharmacist immediately.
In most cases of overdose, people have not reported any side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.
Overdose has been reported to have occurred more frequently when Tamiflu was given to children than to adults and adolescents. Caution should be exercised when preparing liquid Tamiflu for children and when administering Tamiflu capsules or liquid Tamiflu to children.

If you forget to take Tamiflu
Do not take a double dose to make up for a forgotten capsule.

If you stop taking Tamiflu
There are no side effects when you stop Tamiflu. But if Tamiflu is stopped earlier than your doctor told you, the symptoms of flu may come back. Always complete the course that your doctor prescribed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Many of the side effects listed below may also be caused by influenza.

The following serious side effects have been rarely reported since oseltamivir has been marketed:

- Anaphylactic and anaphylactoid reactions: severe allergic reactions, with face and skin swelling, itchy rashes, low blood pressure and breathing difficulties
- Hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice): yellowing of the skin and white of the eyes, change in stool color, changes in behaviour
- Angioneurotic oedema: sudden onset of severe swelling of the skin mainly around the head and neck area, including eyes and tongue, with difficulties breathing
- Stevens-Johnson syndrome and toxic epidermal necrolysis: complicated, possibly life-threatening allergic reaction, severe inflammation of the outer and possibly inner skin, initially with fever, sore throat, and fatigue, skin rashes, leading to blisters, peeling, shedding of larger areas of skin, possible breathing difficulties and low blood pressure
- Gastrointestinal bleeding: prolonged bleeding from the large bowel or spitting up blood
- Neuropsychiatric disorders, as described below.

If you notice any of these symptoms, **get medical help immediately.**

The most frequently (very common and common) reported side effects of Tamiflu are feeling or being sick (nausea, vomiting), stomach ache, stomach upset, headache and pain. These side effects mostly occur after the first dose of the medicine and will usually stop as treatment continues. The frequency of these effects is reduced if the medicinal product is taken with food.

Rare but serious effects: get medical help at once
(*These may affect up to 1 in 1,000 people*)
During Tamiflu treatment, rare events have been reported that include

- Convulsions and delirium, including altered level of consciousness
- Confusion, abnormal behaviour
- Delusions, hallucinations, agitation, anxiety, nightmares

These are reported primarily among children and adolescents and often started suddenly and resolved rapidly. A few cases resulted in self-injury, some with fatal outcome. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Tamiflu.

- Patients, especially children and adolescents, should be closely monitored for the behavioural changes described above.

If you notice any of these symptoms, especially in younger people, **get medical help immediately.**

Adults and adolescents 13 and over

Very common side effects
(may affect more than 1 in 10 people)

- Headache
- Nausea.

Common side effects
(may affect up to 1 in 10 people)

- Bronchitis
- Cold sore virus
- Cough
- Dizziness
- Fever
- Pain
- Pain in limb
- Runny nose
- Sleeping difficulties
- Sore throat
- Stomach ache
- Tiredness
- Upper abdominal fullness
- Upper respiratory tract infections (inflammation of the nose, throat and sinuses)
- Upset stomach
- Vomiting.

Uncommon side effects
(may affect up to 1 in 100 people)

- Allergic reactions
- Altered level of consciousness
- Convulsion
- Heart rhythm abnormalities
- Mild to severe liver function disorders
- Skin reactions (inflammation of the skin, red and itchy rash, scaling skin).

Rare side effects
(may affect up to 1 in 1,000 people)

- Thrombocytopenia (low platelet count)
- Visual disturbances.

Children 1 to 12 years

Very common side effects
(may affect more than 1 in 10 people)

- Cough
- Nasal congestion
- Vomiting.

Common side effects
(may affect up to 1 in 10 people)

- Conjunctivitis (red eyes and discharge or pain in the eye)
- Ear inflammation and other ear disorders
- Headache
- Nausea
- Runny nose
- Stomach ache
- Upper abdominal fullness
- Upset stomach.

Uncommon side effects
(may affect up to 1 in 100 people)
- Inflammation of the skin
- Tympanic membrane (eardrum) disorder.

Infants less than 1 year
The reported side effects in infants 0 to 12 months old are mostly similar to the side effects reported for older children (1 year old or older). Additionally, diarrhoea and diaper rash have been reported.
If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist. However,
- **if you or your child are repeatedly sick,** or
- **if the influenza symptoms get worse or the fever continues**

Tell your doctor as soon as possible.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tamiflu

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25 °C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tamiflu contains
- Each hard capsule contains oseltamivir equivalent to 45 mg of oseltamivir
- The other ingredients are:
  capsule contents: pregelatinised starch, talc, povidone, croscarmellose sodium and sodium stearyl fumarate
  capsule shell: gelatin, black iron oxide (E172) and titanium dioxide (E171)
  printing ink: shellac (E904), titanium dioxide (E171) and FD and C Blue 2 (indigo carmine E132).

What Tamiflu looks like and contents of the pack
The 45 mg hard capsule consists of a grey opaque body bearing the imprint “ROCHE” and a grey opaque cap bearing the imprint “45 mg”. Imprints are blue.

Tamiflu 45 mg hard capsules are available in blister packs of 10.

Marketing Authorisation Holder and Manufacturer

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

Roche Pharma AG
Emil-Barell-Str. 1,
D-79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
N.V. Roche S.A.
Tél/Tel: +32 (0) 2 525 82 11

България
Рош България ЕООД
Тел: +359 2 818 44 44

Česká republika
Roche s. r. o.
Tel: +420 - 2 20382111

Danmark
Roche a/s
Tlf: +45 - 36 39 99 99

Deutschland
Roche Pharma AG
Tel: +49 (0) 7624 140

Eesti
Roche Eesti OÜ
Tel: + 372 - 6 177 380

Ελλάδα
Roche (Hellas) A.E.
Τηλ: +30 210 61 66 100

España
Roche Farma S.A.
Tel: +34 - 91 324 81 00

France
Roche
Tél: +33 (0) 1 47 61 40 00

Hrvatska
Roche d.o.o
Tel: +385 1 4722 333

Lietuva
UAB “Roche Lietuva”
Tel: +370 5 2546799

Luxembourg/Luxemburg
(Voir/siehe Belgique/Belgien)

Magyarország
Roche (Magyarország) Kft.
Tel: +36 - 23 446 800

Malta
(ara Renju Unit)

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438050

Norge
Roche Norge AS
Tlf: +47 - 22 78 90 00

Österreich
Roche Austria GmbH
Tel: +43 (0) 1 27739

Polska
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

Portugal
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

România
Roche România S.R.L.
Tel: +40 21 206 47 01

Ireland
Roche Products (Ireland) Ltd.
Tel: +353 (0) 1 469 0700

Ísland
Roche a/s
c/o Icepharma hf
Sími: +354 540 8000

Italia
Roche S.p.A.
Tel: +39 - 039 2471

Κύπρος
Γ.Α.Σταμάτης & Σια Λτδ.
Τηλ: +357 - 22 76 62 76

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

Slovenija
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

United Kingdom
Roche Products Ltd.
Tel: +44 (0) 1707 366000

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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Information for the user

For people who find it hard to take capsules, including very young children, there's a liquid medicine, *Tamiflu oral suspension*.

If you need a liquid medicine, but it's not available, a suspension can be made up at the pharmacy from Tamiflu capsules (see *Information for healthcare professionals).* This pharmacy preparation is the preferred option.

If the pharmacy preparation is not available either, you can make liquid Tamiflu from these capsules at home.

The dose is the same for treating or preventing flu. The difference is how often it is given.

Making liquid Tamiflu at home

- **If you have the right capsule** for the dose needed (a 45 mg dose), you will open the capsule and stir its contents into one teaspoon (or less) of a suitable sweetened food product. This is usually suitable for children over 1 year. **See the upper set of instructions**.

- **If you need smaller doses,** making liquid Tamiflu from capsules involves extra steps. This is suitable for younger, lighter children and babies: they usually need a Tamiflu dose of less than 45 mg. **See the lower set of instructions**.

Children 1 to 12 years

To make a 45 mg dose, you need:

- **One 45 mg Tamiflu capsule**
- **Sharp scissors**
- **One small bowl**
- **Teaspoon (5 ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of the powder.
  Examples are chocolate or cherry syrup, and dessert toppings such as caramel or fudge sauce. Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Check the dose is correct

To find the correct amount to use, find the patient's weight on the left of the table.
Look at the right column to check the number of capsules you will need to give the patient for a single dose. The amount is the same whether treating or preventing flu.

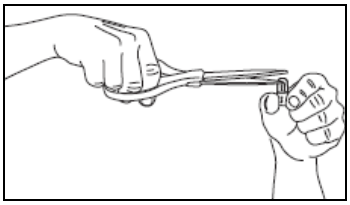
45 mg dose	

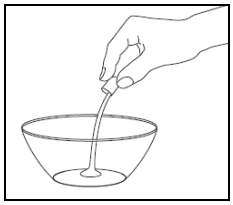
You should use only 45 mg capsules for 45 mg doses. Do not try to make a 30 mg, 60 mg or 75 mg dose by using the contents of 45 mg capsules. Use the appropriate size capsule instead.

Weight	Dose of Tamiflu	Number of capsules
~~Up to 15 kg~~	~~30 mg~~	**Do not use 45 mg capsules**
15 kg up to 23 kg	45 mg	1 capsule
~~23 kg up to 40 kg~~	~~60 mg~~	**Do not use 45 mg capsules**

Step 2: Pour all the powder into a bowl

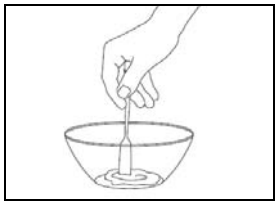
Hold a **45 mg capsule** upright over a bowl and carefully snip off the rounded tip with scissors.
Pour all of the powder into the bowl.
Be careful with the powder, because it may irritate your skin and eyes.





Step 3: Sweeten the powder and give the dose

Add a small amount – no more than one teaspoonful – of sweet food to the powder in the bowl.
This is to hide the bitter taste of the Tamiflu powder.
Stir the mixture well.



Give the whole contents of the bowl to the patient straight away.

If there is some mixture left in the bowl, rinse the bowl with a small amount of water and get the patient to drink it all.

Repeat this procedure every time you need to give the medicine.

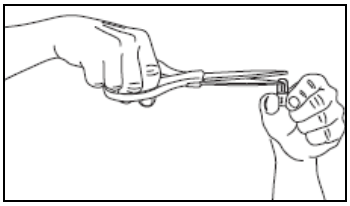
Infants less than 1 year

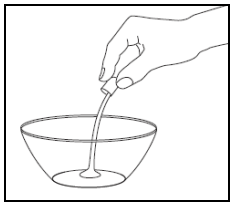
To make a smaller single dose, you need:

- **One 45 mg Tamiflu capsule**
- **Sharp scissors**
  - **Two small bowls** (use separate pairs of bowls for each child)
- **One large oral dose dispenser** to measure out water – a 5 ml dispenser or 10 ml dispenser
- **One small oral dose dispenser** showing measurements of 0.1 ml, to give the dose
- **Teaspoon (5 ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of the Tamiflu.
  Examples are: chocolate or cherry syrup and dessert toppings such as caramel or fudge sauce.
  Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Pour all the powder into a bowl

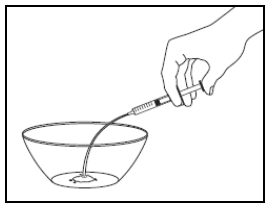
Hold a **45 mg capsule** upright over one of the bowls and carefully snip off the rounded tip with scissors. Be careful with the powder: it may irritate your skin and eyes.
Pour all of the powder into the bowl, whatever the dose you are making.
The amount is the same whether you are treating or preventing flu.





Step 2: Add water to dilute the medicine

Use the larger dispenser draw up **7.5 ml water.**



Add the water to the powder in the bowl.

Stir the mixture with the teaspoon for about 2 minutes.

Don’t worry if not all of the powder dissolves. The undissolved powder is just inactive ingredients.

Step 3: Choose the correct amount for your child’s weight

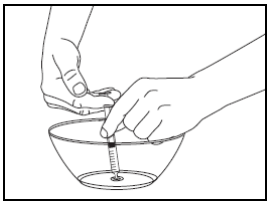
Look up the child’s weight on the left side of the table.
The column on the right of the table shows how much of the liquid mixture you will need to draw up.

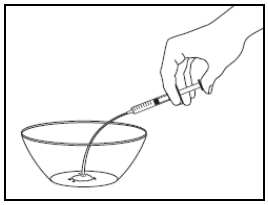
Infants less than 1 year (including full term newborn babies)

Child's weight (nearest)	**How much mixture to draw up**
3 kg	1.5 ml
3.5 kg	1.8 ml
4 kg	2.0 ml
4.5 kg	2.3 ml
5 kg	2.5 ml
5.5 kg	2.8 ml
6 kg	3.0 ml
6.5 kg	3.3 ml
7 kg	3.5 ml
7.5 kg	3.8 ml
8 kg	4.0 ml
8.5 kg	4.3 ml
9 kg	4.5 ml
9.5 kg	4.8 ml
10 kg or more	5.0 ml

Step 4: Draw up the liquid mixture

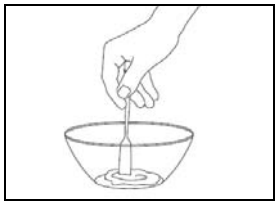
Make sure you have the right size dispenser.
Draw up the correct amount of liquid mixture from the first bowl.
Draw it up carefully so as not to include air bubbles.
Gently squirt the correct dose into the second bowl.





Step 5: Sweeten and give to the child

Add a small amount – no more than one teaspoonful – of a sweet food to the second bowl.
This is to hide the bitter taste of the Tamiflu.
Mix the sweet food and Tamiflu liquid well.



Give the whole contents of the second bowl (Tamiflu liquid mixture with sweet food added) to the child straight away.

If there is anything left in the second bowl, rinse the bowl with a small amount of water and get the child to drink it all. For children unable to drink from a bowl, spoon-feed or use a bottle to feed the child the remaining liquid.

Give the child something to drink.

Throw away any unused liquid left in the first bowl.

Repeat this procedure every time you need to give the medicine.

Information for healthcare professionals only

Patients who are unable to swallow capsules
Commercially manufactured Tamiflu for oral suspension (6mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. In the event thatTamiflu powder for oral suspension is not available, the pharmacist may compound a suspension (6 mg/ml) from Tamiflu capsules. If the pharmacy compounded suspension is also not available, patients may prepare the suspension from capsules at home.

Oral dose dispensers (oral syringes) of appropriate volume and grading should be provided for administering the pharmacy compounded suspension, and for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the dispensers. For home preparation, separate dispensers should be provided for taking the correct volume of water and for measuring the Tamiflu-water mixture. For measuring 5.0 ml of water, dispensers of 5 ml or 10 ml should be used.

The appropriate dispenser sizes for taking the correct volume of Tamiflu suspension (6 mg/ml) are shown below.

Infants less than 1 year (including full term new born babies):

Dose of Tamiflu	Amount of Tamiflu suspension	Dispenser size to use (grading 0.1 ml)
9 mg	1.5 ml	2.0 ml (or 3.0 ml)
10 mg	1.7 ml	2.0 ml (or 3.0 ml)
11.25 mg	1.9 ml	2.0 ml (or 3.0 ml)
12.5 mg	2.1 ml	3.0 ml
13.75 mg	2.3 ml	3.0 ml
15 mg	2.5 ml	3.0 ml
16.25 mg	2.7 ml	3.0 ml
18 mg	3.0 ml	3.0 ml (or 5.0 ml)
19.5 mg	3.3 ml	5.0 ml
21 mg	3.5 ml	5.0 ml
22.5 mg	3.8 ml	5.0 ml
24 mg	4.0 ml	5.0 ml
25.5 mg	4.3 ml	5.0 ml
27 mg	4.5 ml	5.0 ml
28.5 mg	4.8 ml	5.0 ml
30 mg	5.0 ml	5.0 ml

Package Leaflet: Information for the user

Tamiflu 75 mg hard capsules
oseltamivir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. **What Tamiflu is and what it is used for**
2. **What you need to know before you take Tamiflu**
3. **How to take Tamiflu**
4. **Possible side effects**
5. **How to store Tamiflu**
6. **Contents of the pack and other information**

1. What Tamiflu is and what it is used for

- Tamiflu is used for adults, adolescents, children and infants (including full-term newborn babies) for **treating flu** (*influenza*). It can be used when you have flu symptoms, and the flu virus is known to be going round in your community.
- Tamiflu can also be prescribed for adults, adolescents, children and infants above 1 year of age for **preventing flu,** on a case-by-case basis – for instance, if you have been in contact with someone who has flu.
- Tamiflu may be prescribed for adults, adolescents, children and infants (including full-term newborn babies) as **preventive treatment** in exceptional circumstances – for example, if there is a global epidemic of flu (a flu *pandemic*) and the seasonal flu vaccine may not provide sufficient protection.

Tamiflu contains *oseltamivir*, which belongs to a group of medicines named *neuraminidase inhibitors*. These medicines prevent the flu virus from spreading inside the body. They help to ease or prevent the symptoms of the flu virus infection.

Influenza, usually called flu, is an infection caused by a virus. The signs of flu often include a sudden fever (more than 37.8 °C), cough, runny or stuffy nose, headaches, muscle aches and extreme tiredness. These symptoms can also be caused by other infections. True influenza infection only occurs during annual outbreaks (*epidemics*) when flu viruses are spreading in the local community. Outside epidemic periods, flu-like symptoms are usually caused by a different type of illness.

2. What you need to know before you take Tamiflu

Do not take Tamiflu:
- **if you are allergic** (*hypersensitive*) to oseltamivir or any of the other ingredients of Tamiflu listed in section 6**.**

Talk to your doctor if this applies to you. **Do not take Tamiflu.**

Warnings and precautions:
Before you take Tamiflu, make sure the prescribing doctor knows
- if you are **allergic to other medicines**
- if you have **problems with your kidneys**. If so, your dose may need adjustment
- if you have a **severe medical condition**, which may require immediate hospitalisation
- if your **immune system** is not working
- if you have chronic **heart disease** or **respiratory disease**.

During treatment with Tamiflu, **tell a doctor immediately**:
- if you notice changes in behaviour or mood (*neuropsychiatric events*), especially in children and adolescents). These may be signs of rare but serious side effects.

Tamiflu is not a flu vaccine
Tamiflu is not a vaccine: it treats infection, or prevents the flu virus spreading. A vaccine gives you antibodies against the virus. Tamiflu will not change the effectiveness of a flu vaccine, and you might be prescribed both by your doctor.

Other medicines and Tamiflu
Tell your doctor or pharmacist if you are taking any other medicines, or have recently taken any. This includes medicines obtained without a prescription. The following medicines are particularly important:
- chlorpropamide (used to treat diabetes)
- methotrexate (used to treat e.g. rheumatoid arthritis)
- phenylbutazone (used to treat pain and inflammation)
- probenecid (used to treat gout)

Pregnancy and breast-feeding
You must tell your doctor if you are pregnant, if you think you are pregnant or if you are trying to get pregnant so that your doctor can decide if Tamiflu is right for you.

The effects on breast-fed infants are unknown. You must tell your doctor if you are breast-feeding so that your doctor can decide if Tamiflu is right for you.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Tamiflu has no effect on your ability to drive or use machines.

3. How to take Tamiflu

Take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Take Tamiflu as soon as possible, ideally within two days of the flu symptoms starting.

The recommended doses

For treating flu, take two doses daily. It is usually convenient to take one dose in the morning and one in the evening. **It is important to complete the whole 5-day course**, even if you start to feel better quickly.

For preventing flu or after being exposed to an infected person, take one dose daily for 10 days. It is best to take this in the mornings with breakfast.

In special situations, such as widespread flu or for patients with a weak immune system, treatment will continue for up to 6 or 12 weeks.

The recommended dose is based on the patient's body weight. You must use the amount of oral capsules or suspension prescribed by the doctor.

Adults, and adolescents 13 years and over

Body weight	**Treating flu:** dose *for 5 days*	**Preventing flu:** dose *for 10 days*
40 kg or more	75 mg twice daily	75 mg once daily

75 mg can be made up of a 30 mg capsule plus a 45 mg capsule

Children 1 to 12 years

Body weight	**Treating flu:** dose *for 5 days*	**Preventing flu:** dose *for 10 days*
10 to 15 kg	30 mg twice daily	30 mg once daily
More than 15 kg and up to 23 kg	45 mg twice daily	45 mg once daily
More than 23 kg and up to 40 kg	60 mg twice daily	60 mg once daily
More than 40 kg	75 mg twice daily	75 mg once daily

75 mg can be made up of a 30 mg capsule plus a 45 mg capsule

Infants less than 1 year (0 to 12 months)
Giving Tamiflu to infants less than 1 year old for preventing flu during flu pandemic should be based upon the judgment of a doctor after considering the potential benefit versus any potential risk to the infant.

Body weight	**Treating flu:** dose *for 5 days*	**Preventing flu:** dose *for 10 days*
3 kg to 10+ kg,	3 mg per kg body weight, twice daily	3 mg per kg, once daily

mg per kg = *mg for each kilogram of the infant's body weight. For example:*
If a 6-month-old weighs 8 kg, the dose is
8 kg x 3mg per kg = 24 mg

Method of administration
Swallow the capsules whole with water. Do not break or chew the capsules.

Tamiflu can be taken with or without food, although taking it with food can reduce the chance of feeling or being sick (nausea or vomiting).

People who find it hard to take capsules can use a liquid medicine, *Tamiflu oral suspension.* If you need Tamiflu oral suspension, but it's not available from your pharmacy, you can make a liquid form of Tamiflu from these capsules. **See *Making liquid Tamiflu at home,*** over the page.

If you take more Tamiflu than you should
Stop taking Tamiflu and contact a doctor or pharmacist immediately.
In most cases of overdose, people have not reported any side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.
Overdose has been reported to have occurred more frequently when Tamiflu was given to children than to adults and adolescents. Caution should be exercised when preparing liquid Tamiflu for children and when administering Tamiflu capsules or liquid Tamiflu to children.

If you forget to take Tamiflu
Do not take a double dose to make up for a forgotten capsule.

If you stop taking Tamiflu
There are no side effects when you stop Tamiflu. But if Tamiflu is stopped earlier than your doctor told you, the symptoms of flu may come back. Always complete the course that your doctor prescribed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Many of the side effects listed below may also be caused by influenza.

The following serious side effects have been rarely reported since oseltamivir has been marketed:

- Anaphylactic and anaphylactoid reactions: severe allergic reactions, with face and skin swelling, itchy rashes, low blood pressure and breathing difficulties
- Hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice): yellowing of the skin and white of the eyes, change in stool color, changes in behaviour
- Angioneurotic oedema: sudden onset of severe swelling of the skin mainly around the head and neck area, including eyes and tongue, with difficulties breathing
- Stevens-Johnson syndrome and toxic epidermal necrolysis: complicated, possibly life-threatening allergic reaction, severe inflammation of the outer and possibly inner skin, initially with fever, sore throat, and fatigue, skin rashes, leading to blisters, peeling, shedding of larger areas of skin, possible breathing difficulties and low blood pressure
- Gastrointestinal bleeding: prolonged bleeding from the large bowel or spitting up blood
- Neuropsychiatric disorders, as described below.

If you notice any of these symptoms, **get medical help immediately.**

The most frequently (very common and common) reported side effects of Tamiflu are feeling or being sick (nausea, vomiting), stomach ache, stomach upset, headache and pain. These side effects mostly occur after the first dose of the medicine and will usually stop as treatment continues. The frequency of these effects is reduced if the medicinal product is taken with food.

Rare but serious effects: get medical help at once
(*These may affect up to 1 in 1,000 people*)
During Tamiflu treatment, rare events have been reported that include

- Convulsions and delirium, including altered level of consciousness
- Confusion, abnormal behaviour
- Delusions, hallucinations, agitation, anxiety, nightmares

These are reported primarily among children and adolescents and often started suddenly and resolved rapidly. A few cases resulted in self-injury, some with fatal outcome. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Tamiflu.

- Patients, especially children and adolescents, should be closely monitored for the behavioural changes described above.

If you notice any of these symptoms, especially in younger people, **get medical help immediately.**

Adults and adolescents 13 and over

Very common side effects
(may affect more than 1 in 10 people)

- Headache
- Nausea.

Common side effects
(may affect up to 1 in 10 people)

- Bronchitis
- Cold sore virus
- Cough
- Dizziness
- Fever
- Pain
- Pain in limb
- Runny nose
- Sleeping difficulties
- Sore throat
- Stomach ache
- Tiredness
- Upper abdominal fullness
- Upper respiratory tract infections (inflammation of the nose, throat and sinuses)
- Upset stomach
- Vomiting.

Uncommon side effects
(may affect up to 1 in 100 people)

- Allergic reactions
- Altered level of consciousness
- Convulsion
- Heart rhythm abnormalities
- Mild to severe liver function disorders
- Skin reactions (inflammation of the skin, red and itchy rash, scaling skin).

Rare side effects
(may affect up to 1 in 1,000 people)

- Thrombocytopenia (low platelet count)
- Visual disturbances.

Children 1 to 12 years

Very common side effects
(may affect more than 1 in 10 people)

- Cough
- Nasal congestion
- Vomiting.

Common side effects
(may affect up to 1 in 10 people)

- Conjunctivitis (red eyes and discharge or pain in the eye)
- Ear inflammation and other ear disorders
- Headache
- Nausea
- Runny nose
- Stomach ache
- Upper abdominal fullness
- Upset stomach.

Uncommon side effects
(may affect up to 1 in 100 people)
- Inflammation of the skin
- Tympanic membrane (eardrum) disorder.

Infants less than 1 year
The reported side effects in infants 0 to 12 months old are mostly similar to the side effects reported for older children (1 year old or older). Additionally, diarrhoea and diaper rash have been reported..
If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist. However,
- **if you or your child are repeatedly sick,** or
- **if the influenza symptoms get worse or the fever continues**

Tell your doctor as soon as possible.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tamiflu

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 25 °C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tamiflu contains
- Each hard capsule contains oseltamivir equivalent to 75 mg of oseltamivir
- The other ingredients are:
  capsule contents: pregelatinised starch, talc, povidone, croscarmellose sodium and sodium stearyl fumarate
  capsule shell: gelatin, yellow iron oxide (E172), red iron oxide (E172), black iron oxide (E172) and titanium dioxide (E171)
  printing ink: shellac (E904), titanium dioxide (E171) FD and C Blue 2 (indigo carmine E132).

What Tamiflu looks like and contents of the pack
The 75 mg hard capsule consists of a grey opaque body bearing the imprint “ROCHE” and a light yellow opaque cap bearing the imprint “75 mg”. Imprints are blue.

Tamiflu 75 mg hard capsules are available in blister packs of 10.

Marketing Authorisation Holder and Manufacturer

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

Roche Pharma AG
Emil-Barell-Str. 1,
D-79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
N.V. Roche S.A.
Tél/Tel: +32 (0) 2 525 82 11

България
Рош България ЕООД
Тел: +359 2 818 44 44

Česká republika
Roche s. r. o.
Tel: +420 - 2 20382111

Danmark
Roche a/s
Tlf: +45 - 36 39 99 99

Deutschland
Roche Pharma AG
Tel: +49 (0) 7624 140

Eesti
Roche Eesti OÜ
Tel: + 372 - 6 177 380

Ελλάδα
Roche (Hellas) A.E.
Τηλ: +30 210 61 66 100

España
Roche Farma S.A.
Tel: +34 - 91 324 81 00

France
Roche
Tél: +33 (0) 1 47 61 40 00

Hrvatska
Roche d.o.o
Tel: +385 1 4722 333

Lietuva
UAB “Roche Lietuva”
Tel: +370 5 2546799

Luxembourg/Luxemburg
(Voir/siehe Belgique/Belgien)

Magyarország
Roche (Magyarország) Kft.
Tel: +36 - 23 446 800

Malta
(ara Renju Unit)

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438050

Norge
Roche Norge AS
Tlf: +47 - 22 78 90 00

Österreich
Roche Austria GmbH
Tel: +43 (0) 1 27739

Polska
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

Portugal
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

România
Roche România S.R.L.
Tel: +40 21 206 47 01

Ireland
Roche Products (Ireland) Ltd.
Tel: +353 (0) 1 469 0700

Ísland
Roche a/s
c/o Icepharma hf
Sími: +354 540 8000

Italia
Roche S.p.A.
Tel: +39 - 039 2471

Κύπρος
Γ.Α.Σταμάτης & Σια Λτδ.
Τηλ: +357 - 22 76 62 76

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

Slovenija
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

United Kingdom
Roche Products Ltd.
Tel: +44 (0) 1707 366000

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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Information for the user

For people who find it hard to take capsules, including very young children, there's a liquid medicine, *Tamiflu oral suspension*.

If you need a liquid medicine, but it's not available, a suspension can be made up at the pharmacy from Tamiflu capsules (see *Information for healthcare professionals).* This pharmacy preparation is the preferred option.

If the pharmacy preparation is not available either, you can make liquid Tamiflu from these capsules at home.

The dose is the same for treating or preventing flu. The difference is how often it is given.

Making liquid Tamiflu at home

- **If you have the right capsule strength** for the dose needed (a 75 mg dose), you will open the capsule and stir its contents into one teaspoon (or less) of a suitable sweetened food product. This is usually suitable for children over 1 year. **See the upper set of instructions**.

- **If you need smaller doses,** making liquid Tamiflu from capsules involves extra steps. This is suitable for younger children and babies: they usually need a Tamiflu dose of less than 30 mg. **See the lower set of instructions**.

Adults, adolescents 13 years and over, and children weighing 40 kg and over

To make a 75 mg dose, you need:

- **One 75 mg Tamiflu capsule**
- **Sharp scissors**
- **One small bowl**
- **Teaspoon (5 ml spoon)**
- **Water**
- **Sweet food** to hide the bitter taste of the powder.
  Examples are: chocolate or cherry syrup, and dessert toppings such as caramel or fudge sauce. Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Check the dose is correct

To find the correct amount to use, find the patient's weight on the left of the table.
Look at the right column to check the number of capsules you will need to give the patient for a single dose. The amount is the same whether treating or preventing flu.

75 mg dose	

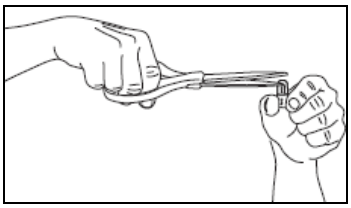
You should use only 75 mg capsules for 75 mg doses. Do not try to make a 75 mg dose by using the contents of 30 mg or 45 mg capsules.

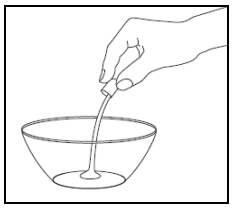
Weight	Dose of Tamiflu	Number of capsules
40 kg and over	75 mg	1 capsule

Not for children who weigh less than 40 kg
You will need to prepare a dose of less than 75 mg for children who weigh less than 40 kg. *See below.*

Step 2: Pour all the powder into a bowl

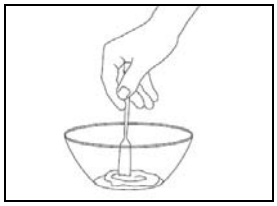
Hold a **75 mg capsule** upright over a bowl and carefully snip off the rounded tip with scissors.
Pour all of the powder into the bowl.
Be careful with the powder, because it may irritate your skin and eyes.





Step 3: Sweeten the powder and give the dose

Add a small amount – no more than one teaspoonful – of sweet food to the powder in the bowl.
This is to hide the bitter taste of the Tamiflu powder.
Stir the mixture well.



Give the whole contents of the bowl to the patient straight away.

If there is some mixture left in the bowl, rinse the bowl with a small amount of water and get the patient to drink it all.

Repeat this procedure every time you need to give the medicine.

Infants less than 1 year, and children weighing less than 40 kg

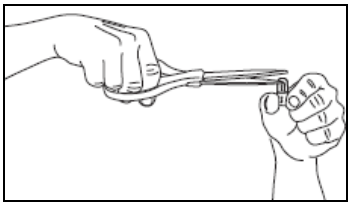
To make a smaller single dose, you need:

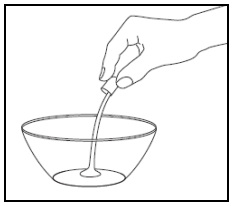
- **One 75 mg Tamiflu capsule**
- **Sharp scissors**
- **Two small bowls**
- **One large oral dose dispenser** to measure out water – a 5 or 10 ml dispenser
- **One small oral dose dispenser** showing measurements of 0.1 ml, to give the dose
- **Teaspoon (5 ml spoon)**
- **Water**

- **Sweet food** to hide the bitter taste of the Tamiflu.
  Examples are: chocolate or cherry syrup and dessert toppings such as caramel or fudge sauce.
  Or you can make sugar water: mix a teaspoon of water with three-quarters (3/4) of a teaspoon of sugar.

Step 1: Pour all the powder into a bowl

Hold a **75 mg capsule** upright over one of the bowls and carefully snip off the rounded tip with scissors. Be careful with the powder: it may irritate your skin and eyes.
Pour all of the powder into the bowl, whatever the dose you are making.
The amount is the same whether you are treating or preventing flu.

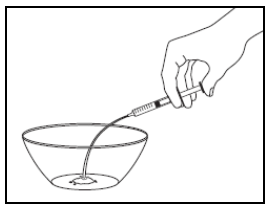




Step 2: Add water to dilute the medicine

Use the larger dispenser to draw up 12.5 ml water.

Add the water to the powder in the bowl.



Stir the mixture with the teaspoon for about 2 minutes.

Don’t worry if not all of the powder dissolves. The undissolved powder is just inactive ingredients.

Step 3: Choose the correct amount for your child’s weight

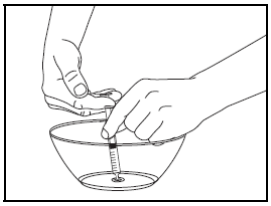
Look up the child’s weight on the left side of the table.
The column on the right of the table shows how much of the liquid mixture you will need to draw up.

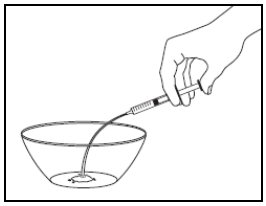
Infants less than 1 year (including full-term newborn babies)

Child's weight (nearest)	**How much mixture to draw up**
3 kg	1.5 ml
3.5 kg	1.8 ml
4 kg	2.0 ml
4.5 kg	2.3 ml
5 kg	2.5 ml
5.5 kg	2.8 ml
6 kg	3.0 ml
6.5 kg	3.3 ml
7 kg	3.5 ml
7.5 kg	3.8 ml
8 kg	4.0 ml
8.5 kg	4.3 ml
9 kg	4.5 ml
9.5 kg	4.8 ml
10 kg or more	5.0 ml

Step 4: Draw up the liquid mixture

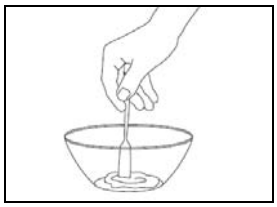
Make sure you have the right size dispenser.
Draw up the correct amount of liquid mixture from the first bowl.
Draw it up carefully so as not to include air bubbles.
Gently squirt the correct dose into the second bowl.





Step 5: Sweeten and give to the child

Add a small amount – no more than one teaspoonful – of a sweet food to the second bowl.
This is to hide the bitter taste of the Tamiflu.
Mix the sweet food and Tamiflu liquid well.



Give the whole contents of the second bowl (Tamiflu liquid mixture with sweet food added) to the child straight away.

If there is anything left in the second bowl, rinse the bowl with a small amount of water and get the child to drink it all. For children unable to drink from a bowl, spoon-feed or use a bottle to feed the child the remaining liquid.

Give the child something to drink.

Throw away any unused liquid left in the first bowl.

Repeat this procedure every time you need to give the medicine.

Information for healthcare professionals only

Patients who are unable to swallow capsules:
Commercially manufactured Tamiflu for oral suspension (6mg/ml) is the preferred product for paediatric and adult patients who have difficulties swallowing capsules or where lower doses are needed. In the event thatTamiflu powder for oral suspension is not available, the pharmacist may compound a suspension (6 mg/ml) from Tamiflu capsules. If the pharmacy compounded suspension is also not available, patients may prepare the suspension from capsules at home.

Oral dose dispensers (oral syringes) of appropriate volume and grading should be provided for administering the pharmacy compounded suspension, and for the procedures involved in the home preparation. In both cases, the correct volumes should preferably be marked on the dispensers. For home preparation, separate dispensers should be provided for taking the correct volume of water and for measuring the Tamiflu-water mixture. For measuring 12.5 ml of water a 10 ml dispenser should be used.

The appropriate dispenser sizes for taking the correct volume of Tamiflu suspension (6 mg/ml) are shown below.

Infants less than 1 year (including full-term new born babies):

Dose of Tamiflu	Amount of Tamiflu suspension	Dispenser size to use (grading 0.1 ml)
9 mg	1.5 ml	2.0 ml (or 3.0 ml)
10 mg	1.7 ml	2.0 ml (or 3.0 ml)
11.25 mg	1.9 ml	2.0 ml (or 3.0 ml)
12.5 mg	2.1 ml	3.0 ml
13.75 mg	2.3 ml	3.0 ml
15 mg	2.5 ml	3.0 ml
16.25 mg	2.7 ml	3.0 ml
18 mg	3.0 ml	3.0 ml (or 5.0 ml)
19.5 mg	3.3 ml	5.0 ml
21 mg	3.5 ml	5.0 ml
22.5 mg	3.8 ml	5.0 ml
24 mg	4.0 ml	5.0 ml
25.5 mg	4.3 ml	5.0 ml
27 mg	4.5 ml	5.0 ml
28.5 mg	4.8 ml	5.0 ml
30 mg	5.0 ml	5.0 ml

Children 1 year or older, weighing less than 40 kg:

Dose of Tamiflu	Amount of Tamiflu suspension	Dispenser size to use (grading 0.1 ml)
30 mg	5.0 ml	5.0 ml (or 10.0 ml)
45 mg	7.5 ml	10.0 ml
60 mg	10.0 ml	10.0 ml

Package Leaflet: Information for the user

Tamiflu 6 mg/ml powder for oral suspension
oseltamivir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. **What Tamiflu is and what it is used for**
2. **What you need to know before you take Tamiflu**
3. **How to take Tamiflu**
4. **Possible side effects**
5. **How to store Tamiflu**
6. **Contents of the pack and other information**

1. What Tamiflu is and what it is used for

- Tamiflu is used for adults, adolescents, children and infants (including full-term newborn babies) for **treating flu** (*influenza*). It can be used when you have flu symptoms, and the flu virus is known to be going round in your community.
- Tamiflu can also be prescribed for adults, adolescents, children and infants above 1 year of age for **preventing flu,** on a case-by-case basis – for instance, if you have been in contact with someone who has flu.
- Tamiflu may be prescribed for adults, adolescents, children and infants (including full-term newborn babies) as **preventive treatment** in exceptional circumstances – for example, if there is a global epidemic of flu (a flu *pandemic*) and the seasonal flu vaccine may not provide sufficient protection.

Tamiflu contains *oseltamivir*, which belongs to a group of medicines named *neuraminidase inhibitors*. These medicines prevent the flu virus from spreading inside the body. They help to ease or prevent the symptoms of the flu virus infection.

Influenza, usually called flu, is an infection caused by a virus. The signs of flu often include a sudden fever (more than 37.8 °C), cough, runny or stuffy nose, headaches, muscle aches and extreme tiredness. These symptoms can also be caused by other infections. True influenza infection only occurs during annual outbreaks (*epidemics*) when flu viruses are spreading in the local community. Outside epidemic periods, flu-like symptoms are usually caused by a different type of illness.

2. What you need to know before you take Tamiflu

Do not take Tamiflu:
- **if you are allergic** (*hypersensitive*) to oseltamivir or any of the other ingredients of Tamiflu listed in section 6**.**

Talk to your doctor if this applies to you. **Do not take Tamiflu.**

Warnings and precautions:
Before you take Tamiflu, make sure the prescribing doctor knows
- if you are **allergic to other medicines**
- if you have **problems with your kidneys**. If so, your dose may need adjustment
- if you have a **severe medical condition**, which may require immediate hospitalisation
- if your **immune system** is not working
- if you have chronic **heart disease** or **respiratory disease**.

During treatment with Tamiflu, **tell a doctor immediately**:
- if you notice changes in behaviour or mood (*neuropsychiatric events*), especially in children and adolescents). These may be signs of rare but serious side effects.

Tamiflu is not a flu vaccine
Tamiflu is not a vaccine: it treats infection, or prevents the flu virus spreading. A vaccine gives you antibodies against the virus. Tamiflu will not change the effectiveness of a flu vaccine, and you might be prescribed both by your doctor.

Other medicines and Tamiflu
Tell your doctor or pharmacist if you are taking any other medicines, or have recently taken any. This includes medicines obtained without a prescription. The following medicines are particularly important:
- chlorpropamide (used to treat diabetes)
- methotrexate (used to treat e.g. rheumatoid arthritis)
- phenylbutazone (used to treat pain and inflammation)
- probenecid (used to treat gout)

Pregnancy and breast-feeding
You must tell your doctor if you are pregnant, if you think you are pregnant or if you are trying to get pregnant so that your doctor can decide if Tamiflu is right for you.

The effects on breast-fed infants are unknown. You must tell your doctor if you are breast-feeding so that your doctor can decide if Tamiflu is right for you.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Tamiflu has no effect on your ability to drive or use machines.

Tamiflu contains fructose
Before you take Tamiflu, make sure your prescribing doctor knows if you have hereditary fructose intolerance. This medicine contains sorbitol, which is a form of fructose.
Sorbitol can have a mild laxative effect.

3. How to take Tamiflu

Take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Always use the oral dispenser that is provided in the box and has markings indicating the dose in millilitres (ml).

Take Tamiflu as soon as possible, ideally within two days of the flu symptoms starting.

The recommended doses

For treating flu, take two doses daily. It is usually convenient to take one dose in the morning and one in the evening. **It is important to complete the whole 5-day course**, even if you start to feel better quickly.

For preventing flu or after being exposed to an infected person, take one dose daily for 10 days. It is best to take this in the mornings with breakfast.

In special situations, such as widespread flu, or for patients with a weak immune system, treatment will continue for up to 6 or 12 weeks.

The recommended dose is based on the patient's body weight. You must use the amount of Tamiflu prescribed by the doctor. The oral suspension can be used by people who find it hard to take capsules. See the instructions overleaf to make up and give a dose.

Adults, and adolescents 13 years and over

Body weight	**Treating flu:** dose for *5 days*	**Preventing flu:** dose for *10 days*
40 kg or more	12.5 ml twice daily	12.5 ml once daily

12.5 ml *is made up of a 5* ml *dose plus a 7.5* ml *dose*

Children 1 to 12 years

Body weight	**Treating flu:** dose for *5 days*	**Preventing flu:** dose for *10 days*
10 kg to 15 kg	5.0 ml twice daily	5.0 ml once daily
More than 15 kg, up to 23 kg	7.5 ml twice daily	7.5 ml once daily
More than 23 kg, up to 40 kg	10.0 ml twice daily	10.0 ml once daily
More than 40 kg	12.5 ml twice daily	12.5 ml once daily

Infants less than 1 year (0 to 12 months)
Giving Tamiflu to infants less than 1 year old for preventing flu during flu pandemic should be based upon the judgment of a doctor after considering the potential benefit versus any potential risk to the infant.
A 3 ml oral dispenser (graduated in 0.1 ml steps) should be used for dosing infants less than 1 year old requiring 1 to 3 ml of Tamiflu oral suspension.

Body weight	**Treating flu:** dose for *5 days*	**Preventing flu:** dose for *10 days*	Dispenser size to use
3 kg	1.5 ml twice daily	1.5 ml once daily	3 ml
3.5 kg	1.8 ml twice daily	1.8 ml once daily	3 ml
4 kg	2.0 ml twice daily	2.0 ml once daily	3 ml
4.5 kg	2.3 ml twice daily	2.3 ml once daily	3 ml
5 kg	2.5 ml twice daily	2.5 ml once daily	3 ml
5.5 kg	2.8 ml twice daily	2.8 ml once daily	3 ml
6 kg	3.0 ml twice daily	3.0 ml once daily	3 ml
> 6 to 7 kg	3.5 ml twice daily	3.5 ml once daily	10 ml
> 7 to 8 kg	4.0 ml twice daily	4.0 ml once daily	10 ml
> 8 to 9 kg	4.5 ml twice daily	4.5 ml once daily	10 ml
> 9 to 10 kg	5.0 ml twice daily	5.0 ml once daily	10 ml

If you take more Tamiflu than you should
Stop taking Tamiflu and contact a doctor or pharmacist immediately.
In most cases of overdose, people have not reported any side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.
Overdose has been reported to have occurred more frequently when Tamiflu was given to children than to adults and adolescents. Caution should be exercised when preparing liquid Tamiflu for children and when administering Tamiflu capsules or liquid Tamiflu to children.

If you forget to take Tamiflu
Do not take a double dose to make up for a forgotten dose.

If you stop taking Tamiflu
There are no side effects when you stop Tamiflu. But if Tamiflu is stopped earlier than your doctor told you, the symptoms of flu may come back. Always complete the course that your doctor prescribed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Many of the side effects listed below may also be caused by influenza.

The following serious side effects have been rarely reported since oseltamivir has been marketed:
- Anaphylactic and anaphylactoid reactions: severe allergic reactions, with face and skin swelling, itchy rashes, low blood pressure and breathing difficulties
- Hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice): yellowing of the skin and white of the eyes, change in stool color, changes in behaviour
- Angioneurotic oedema: sudden onset of severe swelling of the skin mainly around the head and neck area, including eyes and tongue, with difficulties breathing
- Stevens-Johnson syndrome and toxic epidermal necrolysis: complicated, possibly life-threatening allergic reaction, severe inflammation of the outer and possibly inner skin, initially with fever, sore throat, and fatigue, skin rashes, leading to blisters, peeling, shedding of larger areas of skin, possible breathing difficulties and low blood pressure
- Gastrointestinal bleeding: prolonged bleeding from the large bowel or spitting up blood
- Neuropsychiatric disorders, as described below.

If you notice any of these symptoms, **get medical help immediately.**

The most frequently (very common and common) reported side effects of Tamiflu are feeling or being sick (nausea, vomiting), stomach ache, stomach upset, headache and pain. These side effects mostly occur after the first dose of the medicine and will usually stop as treatment continues. The frequency of these effects is reduced if the medicinal product is taken with food.

Rare but serious effects: get medical help at once
(*These may affect up to 1 in 1,000 people*)
During Tamiflu treatment, rare events have been reported that include
- Convulsions and delirium, including altered level of consciousness
- Confusion, abnormal behaviour
- Delusions, hallucinations, agitation, anxiety, nightmares

These are reported primarily among children and adolescents and often started suddenly and resolved rapidly. A few cases resulted in self-injury, some with fatal outcome. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Tamiflu.
- Patients, especially children and adolescents, should be closely monitored for the behavioural changes described above.

If you notice any of these symptoms, especially in younger people, **get medical help immediately.**

Adults and adolescents 13 and over

Very common side effects
(may affect more than 1 in 10 people)
- Headache
- Nausea.

Common side effects
(may affect up to 1 in 10 people)
- Bronchitis
- Cold sore virus
- Cough
- Dizziness
- Fever
- Pain
- Pain in limb
- Runny nose
- Sleeping difficulties
- Sore throat
- Stomach ache
- Tiredness
- Upper abdominal fullness
- Upper respiratory tract infections (inflammation of the nose, throat and sinuses)
- Upset stomach
- Vomiting.

Uncommon side effects
(may affect up to 1 in 100 people)
- Allergic reactions
- Altered level of consciousness
- Convulsion
- Heart rhythm abnormalities
- Mild to severe liver function disorders
- Skin reactions (inflammation of the skin, red and itchy rash, scaling skin).

Rare side effects
(may affect up to 1 in 1,000 people)
- Thrombocytopenia (low platelet count)
- Visual disturbances.

Children 1 to 12 years

Very common side effects
(may affect more than 1 in 10 people)
- Cough
- Nasal congestion
- Vomiting.

Common side effects
(may affect up to 1 in 10 people)
- Conjunctivitis (red eyes and discharge or pain in the eye)
- Ear inflammation and other ear disorders
- Headache
- Nausea

- Runny nose
- Stomach ache
- Upper abdominal fullness
- Upset stomach.

Uncommon side effects
(may affect up to 1 in 100 people)
- Inflammation of the skin
- Tympanic membrane (eardrum) disorder.

Infants less than 1 year
The reported side effects in infants 0 to 12 months old are mostly similar to the side effects reported for older children (1 year old or older). Additionally, diarrhoea and diaper rash have been reported.
If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist. However,
- **if you or your child are repeatedly sick,** or
- **if the influenza symptoms get worse or the fever continues**

Tell your doctor as soon as possible.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tamiflu

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.

Powder: Do not store above 30°C.
After reconstitution, store below 25 °C for 10 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tamiflu contains

- The active substance is oseltamivir (6 mg/ml oseltamivir after reconstitution).
- The other ingredients are sorbitol (E420), sodium dihydrogen citrate (E331[a]), xanthan gum (E415), sodium benzoate (E211), saccharin sodium (E954), titanium dioxide (E171) and tutti frutti flavour (including maltodextrins [maize], propylene glycol, arabic gum E414 and natural identical flavouring substances [mainly consisting of banana, pineapple and peach flavour]).

What Tamiflu looks like and contents of the pack

Powder for oral suspension

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

Tamiflu 6 mg/ml powder for oral suspension is available in a bottle containing 13 g powder for mixing with 55 ml of water.

The box also contains 1 plastic measuring jug (55 ml), 1 plastic bottle adapter (to help get the drug into the dispenser),1 plastic 3 ml oral dispenser and 1 plastic 10 ml oral dispenser (to give the correct amount of medicine via the mouth). Shown on the oral dispenser are millilitre (ml) markings of the medicine (see figures in *Instructions for the user*).

For details on how to prepare the oral suspension and how to measure and take the medicine, read *Instructions for the user,* over the page.

Marketing Authorisation Holder and Manufacturer

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

Roche Pharma AG
Emil-Barell-Str. 1,
D-79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
N.V. Roche S.A.
Tél/Tel: +32 (0) 2 525 82 11

България
Рош България ЕООД
Тел: +359 2 818 44 44

Česká republika
Roche s. r. o.
Tel: +420 - 2 20382111

Danmark
Roche a/s
Tlf: +45 - 36 39 99 99

Deutschland
Roche Pharma AG
Tel: +49 (0) 7624 140

Eesti
Roche Eesti OÜ
Tel: + 372 - 6 177 380

Ελλάδα
Roche (Hellas) A.E.
Τηλ: +30 210 61 66 100

Lietuva
UAB “Roche Lietuva”
Tel: +370 5 2546799

Luxembourg/Luxemburg
(Voir/siehe Belgique/Belgien)

Magyarország
Roche (Magyarország) Kft.
Tel: +36 - 23 446 800

Malta
(ara Renju Unit)

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438050

Norge
Roche Norge AS
Tlf: +47 - 22 78 90 00

Österreich
Roche Austria GmbH
Tel: +43 (0) 1 27739

España
Roche Farma S.A.
Tel: +34 - 91 324 81 00

France
Roche
Tél: +33 (0) 1 47 61 40 00

Hrvatska
Roche d.o.o
Tel: +385 1 4722 333

Ireland
Roche Products (Ireland) Ltd.
Tel: +353 (0) 1 469 0700

Ísland
Roche a/s
c/o Icepharma hf
Sími: +354 540 8000

Italia
Roche S.p.A.
Tel: +39 - 039 2471

Κύπρος
Γ.Α.Σταμάτης & Σια Λτδ.
Τηλ: +357 - 22 76 62 76

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

Polska
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

Portugal
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

România
Roche România S.R.L.
Tel: +40 21 206 47 01

Slovenija
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

United Kingdom
Roche Products Ltd.
Tel: +44 (0) 1707 366000

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Instructions for the user

There are two stages to taking Tamiflu oral suspension.

Stage 1 Prepare a new bottle of the medicine

Your pharmacist may have prepared the medicine for you when you collected your prescription. If not, you can do it easily yourself. See the first set of instructions. **You only need to do this once,** at the beginning of your course.

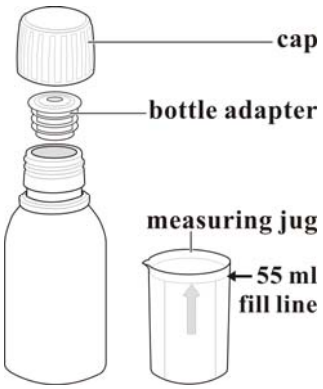
Stage 2 Measure and give the correct dose

Shake the suspension well and draw the appropriate recommended dose into the dispenser. See the second set of instructions. You will need to do this every time you need a dose.

Stage 1: Prepare a new bottle of the medicine

You will need:

- The bottle, containing Tamiflu powder (in the medicine pack)
- The bottle cap (in the medicine pack)
- A plastic measuring jug (in the medicine pack)
- The plastic bottle adapter (in the medicine pack)
- Water



- **Tap the bottle to loosen the powder**
  Tap the closed bottle gently several times to loosen the powder.

- **Use the jug to measure 55 ml of water**
  The measuring jug in the pack has a line marked to show you an exact amount.
  Fill it with water to the indicated level.

- **Add all the water, close and shake**
  Pour all of the water from the jug into the bottle, onto the powder.
  Always use 55 ml of water, whatever the dose you need.
  Put the cap back on the bottle. Shake the bottle well for 15 seconds.

- **Press in the adapter**
  Open the bottle and press the bottle adapter hard into the neck of the bottle.

- **Close the bottle again**
  Screw the cap tightly onto the top of the bottle, which now includes the adapter.
  This will make sure that the bottle adapter fits in the bottle in the right position.

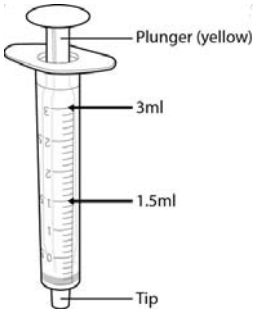
You now have a bottle of Tamiflu oral suspension ready to measure out a dose. You will not need to prepare it again unless you start a new bottle.

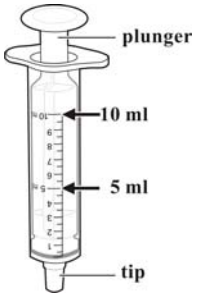
Stage 2: Measure and give the correct dose

You will need:

- **A bottle of prepared Tamiflu oral suspension**
- **Depending on the required dose you will need the 3 ml oral dispenser (yellow plunger, 0.1 ml graduation) or the 10 ml oral dispenser (white plunger 0.5 ml graduation) from the medicine pack**.
- For doses from 1.0 ml to 3.0 ml, the 3 ml oral dispenser should be used. For doses above 3.0 ml to 10 ml, 10 ml oral dispenser should be used.

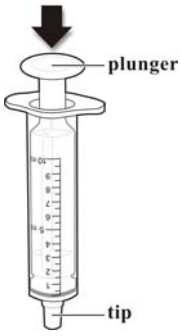
Always use the oral dispenser provided with your medicine to measure a correct dose.



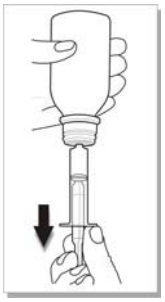


- **Shake the bottle**
  Check the cap is secure, and then shake the bottle of Tamiflu oral suspension.
  Always shake well before use.

- **Prepare the oral dispenser**
  Depending on the required dose, use the 3 ml dispenser (yellow plunger) or the 10 ml oral dispenser (white plunger) provided in the pack.
  Push the plunger completely down toward the tip of the dispenser.



- **Fill the dispenser with the correct dose**
  Unscrew the cap from the bottle.
  Push the tip of the dispenser into the bottle adapter.
  Then **turn the whole unit upside down** (bottle and dispenser together).



Slowly pull out the plunger to draw medicine into the dispenser.
Stop at the mark that shows the dose you need.
Turn the whole unit upright.
Remove the dispenser from the bottle.

- **Give the medicine into the mouth**
  Deliver the suspension directly into the mouth by pushing down the plunger of the dispenser.
  Make sure the medicine is swallowed.
  You may drink and eat something after taking the medicine.

- **Close the bottle, keep it safe**
  Put the cap back on the bottle. Keep it out of sight and reach of children.

  Store the medicine below 25 º C for up to 10 days. See 5 *How to store Tamiflu*, overleaf.

Take the dispenser apart straight after dosing, and rinse both parts of the dispenser under running tap water.

Package Leaflet: Information for the user

Tamiflu 12 mg/ml powder for oral suspension
oseltamivir

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. **What Tamiflu is and what it is used for**
2. **What you need to know before you take Tamiflu**
3. **How to take Tamiflu**
4. **Possible side effects**
5. **How to store Tamiflu**
6. **Contents of the pack and other information**

1. What Tamiflu is and what it is used for

- Tamiflu is used for adults, adolescents, children and infants (including full-term newborn babies) for **treating flu** (*influenza*). It can be used when you have flu symptoms, and the flu virus is known to be going round in your community.
- Tamiflu can also be prescribed for adults, adolescents, children and infants above 1 year of age for **preventing flu,** on a case-by-case basis – for instance, if you have been in contact with someone who has flu.
- Tamiflu may be prescribed for adults, adolescents, children and infants (including full-term newborn babies) as **preventive treatment** in exceptional circumstances – for example, if there is a global epidemic of flu (a flu *pandemic*) and the seasonal flu vaccine may not provide sufficient protection.

Tamiflu contains *oseltamivir*, which belongs to a group of medicines named *neuraminidase inhibitors*. These medicines prevent the flu virus from spreading inside the body. They help to ease or prevent the symptoms of the flu virus infection.

Influenza, usually called flu, is an infection caused by a virus. The signs of flu often include a sudden fever (more than 37.8 °C), cough, runny or stuffy nose, headaches, muscle aches and extreme tiredness. These symptoms can also be caused by other infections. True influenza infection only occurs during annual outbreaks (*epidemics*) when flu viruses are spreading in the local community. Outside epidemic periods, flu-like symptoms are usually caused by a different type of illness.

2. What you need to know before you take Tamiflu

Do not take Tamiflu:
- **if you are allergic** (*hypersensitive*) to oseltamivir or any of the other ingredients of Tamiflu listed in section 6**.**

Talk to your doctor if this applies to you. **Do not take Tamiflu.**

Warnings and precautions:
Before you take Tamiflu, make sure the prescribing doctor knows
- if you are **allergic to other medicines**
- if you have **problems with your kidneys**. If so, your dose may need adjustment
- if you have a **severe medical condition**, which may require immediate hospitalisation
- if your **immune system** is not working
- if you have chronic **heart disease** or **respiratory disease**.

During treatment with Tamiflu, **tell a doctor immediately**:
- if you notice changes in behaviour or mood (*neuropsychiatric events*), especially in children and adolescents). These may be signs of rare but serious side effects.

Tamiflu is not a flu vaccine
Tamiflu is not a vaccine: it treats infection, or prevents the flu virus spreading. A vaccine gives you antibodies against the virus. Tamiflu will not change the effectiveness of a flu vaccine, and you might be prescribed both by your doctor.

Other medicines and Tamiflu
Tell your doctor or pharmacist if you are taking any other medicines, or have recently taken any. This includes medicines obtained without a prescription. The following medicines are particularly important:
- chlorpropamide (used to treat diabetes)
- methotrexate (used to treat e.g. rheumatoid arthritis)
- phenylbutazone (used to treat pain and inflammation)
- probenecid (used to treat gout)

Pregnancy and breast-feeding
You must tell your doctor if you are pregnant, if you think you are pregnant or if you are trying to get pregnant so that your doctor can decide if Tamiflu is right for you.

The effects on breast-fed infants are unknown. You must tell your doctor if you are breast-feeding so that your doctor can decide if Tamiflu is right for you.

Ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Tamiflu has no effect on your ability to drive or use machines.

Tamiflu contains fructose
Before you take Tamiflu, make sure your prescribing doctor knows if you have hereditary fructose intolerance. This medicine contains sorbitol, which is a form of fructose.
Sorbitol can have a mild laxative effect.

3. How to take Tamiflu

Take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Always use the oral dispenser that is provided in the box and has markings indicating the dose in milligrams (mg).

Take Tamiflu as soon as possible, ideally within two days of flu symptoms starting.

The recommended doses

For treating flu, take two doses daily. It is usually convenient to take one dose in the morning and one in the evening. **It is important to complete the whole 5-day course**, even if you start to feel better quickly.

For preventing flu or after being exposed to an infected person, take one dose daily for 10 days. It is best to take this in the mornings with breakfast.

In special situations, such as widespread flu, or for patients with a weak immune system, treatment will continue for up to 6 or 12 weeks.

The recommended dose is based on the patient's body weight. You must use the amount of Tamiflu prescribed by the doctor. The oral suspension can be used by people who find it hard to take capsules. See the instructions overleaf to make up and give a dose.

Adults, and adolescents 13 years and over

Body weight	**Treating flu:** dose for *5 days*	**Preventing flu:** dose for *10 days*
40 kg or more	75 mg twice daily	75 mg once daily

75 mg is made up of a 30 mg dose plus a 45 mg dose

Children 1 to 12 years

Body weight	**Treating flu:** dose for *5 days*	**Preventing flu:** dose for *10 days*
10 kg to 15 kg	30 mg twice daily	30 mg once daily
More than 15 kg, up to 23 kg	45 mg twice daily	45 mg once daily
More than 23 kg, up to 40 kg	60 mg twice daily	60 mg once daily
More than 40 kg	75 mg twice daily	75 mg once daily

75 mg is made up of a 30 mg dose plus a 45 mg dose

Infants less than 1 year
This formulation is not suitable for infants less than 1 year old.

If you take more Tamiflu than you should
Stop taking Tamiflu and
contact a doctor or pharmacist immediately.
In most cases of overdose, people have not reported any side effects. When side effects were reported, they were similar to those from normal doses, as listed in section 4.
Overdose has been reported to have occurred more frequently when Tamiflu was given to children than to adults and adolescents. Caution should be exercised when preparing liquid Tamiflu for children and when administering Tamiflu capsules or liquid Tamiflu to children.

If you forget to take Tamiflu
Do not take a double dose to make up for a forgotten dose.

If you stop taking Tamiflu
There are no side effects when you stop Tamiflu. But if Tamiflu is stopped earlier than your doctor told you, the symptoms of flu may come back. Always complete the course that your doctor prescribed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Many of the side effects listed below may also be caused by influenza.

The following serious side effects have been rarely reported since oseltamivir has been marketed:

- Anaphylactic and anaphylactoid reactions: severe allergic reactions, with face and skin swelling, itchy rashes, low blood pressure and breathing difficulties
- Hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice): yellowing of the skin and white of the eyes, change in stool color, changes in behaviour
- Angioneurotic oedema: sudden onset of severe swelling of the skin mainly around the head and neck area, including eyes and tongue, with difficulties breathing
- Stevens-Johnson syndrome and toxic epidermal necrolysis: complicated, possibly life-threatening allergic reaction, severe inflammation of the outer and possibly inner skin, initially with fever, sore throat, and fatigue, skin rashes, leading to blisters, peeling, shedding of larger areas of skin, possible breathing difficulties and low blood pressure
- Gastrointestinal bleeding: prolonged bleeding from the large bowel or spitting up blood
- Neuropsychiatric disorders, as described below.

If you notice any of these symptoms, **get medical help immediately.**

The most frequently (very common and common) reported side effects of Tamiflu are feeling or being sick (nausea, vomiting), stomach ache, stomach upset, headache and pain. These side effects mostly occur after the first dose of the medicine and will usually stop as treatment continues. The frequency of these effects is reduced if the medicinal product is taken with food.

Rare but serious effects: get medical help at once
(*These may affect up to 1 in 1,000 people*)
During Tamiflu treatment, rare events have been reported that include

- Convulsions and delirium, including altered level of consciousness
- Confusion, abnormal behaviour
- Delusions, hallucinations, agitation, anxiety, nightmares

These are reported primarily among children and adolescents and often started suddenly and resolved rapidly. A few cases resulted in self-injury, some with fatal outcome. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Tamiflu.

- Patients, especially children and adolescents, should be closely monitored for the behavioural changes described above.

If you notice any of these symptoms, especially in younger people, **get medical help immediately.**

Adults, and adolescents 13 and over

Very common side effects
(may affect more than 1 in 10 people)

- Headache
- Nausea.

Common side effects
(may affect up to 1 in 10 people)

- Bronchitis
- Cold sore virus
- Cough
- Dizziness
- Fever
- Pain

- Pain in limb
- Runny nose
- Sleeping difficulties
- Sore throat
- Stomach ache
- Tiredness
- Upper abdominal fullness
- Upper respiratory tract infections (inflammation of the nose, throat and sinuses)
- Upset stomach
- Vomiting.

Uncommon side effects
(may affect up to 1 in 100 people)
- Allergic reactions
- Altered level of consciousness
- Convulsion
- Heart rhythm abnormalities
- Mild to severe liver function disorders
- Skin reactions (inflammation of the skin, red and itchy rash, scaling skin).

Rare side effects
(may affect up to 1 in 1,000 people)
- Thrombocytopenia (low platelet count)
- Visual disturbances.

Children 1 to 12 years

Very common side effects
(may affect more than 1 in 10 people)
- Cough
- Nasal congestion
- Vomiting.

Common side effects
(may affect up to 1 in 10 people)
- Conjunctivitis (red eyes and discharge or pain in the eye)
- Ear inflammation and other ear disorders
- Headache
- Nausea
- Runny nose
- Stomach ache
- Upper abdominal fullness
- Upset stomach.

Uncommon side effects
(may affect up to 1 in 100 people)
- Inflammation of the skin
- Tympanic membrane (eardrum) disorder.

Infants less than 1 year
The reported side effects in infants 0 to 12 months old are mostly similar to the side effects reported for older children (1 year old or older). Additionally, diarrhoea and diaper rash have been reported.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist. However,

- **if you or your child are repeatedly sick,** or
- **if the influenza symptoms get worse or the fever continues**

Tell your doctor as soon as possible.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tamiflu

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.

Powder: Do not store above 30°C.
After reconstitution, store below 25 °C for 10 days or in a refrigerator (2 °C - 8 °C) for 17 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tamiflu contains

- The active substance is oseltamivir (12 mg/ml oseltamivir after reconstitution).
- The other ingredients are sorbitol (E420), sodium dihydrogen citrate (E331[a]), xanthan gum (E415), sodium benzoate (E211), saccharin sodium (E954), titanium dioxide (E171) and tutti frutti flavour (including maltodextrins [maize], propylene glycol, arabic gum E414 and natural identical flavouring substances [mainly consisting of banana, pineapple and peach flavour]).

What Tamiflu looks like and contents of the pack

Powder for oral suspension

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

Tamiflu 12 mg/ml powder for oral suspension is available in a bottle containing 30 g powder for mixing with 52 ml of water.

The box also contains 1 plastic measuring jug (52 ml), 1 plastic bottle adapter (to help get the drug into the dispenser) and 1 plastic oral dispenser (to give the correct amount of medicine via the mouth). Shown on the oral dispenser are marks for 30 mg, 45 mg and 60 mg of the medicine (see figures in *Instructions for the user*).

For details on how to prepare the oral suspension and how to measure and take the medicine, read *Instructions for the user*, over the page.

Marketing Authorisation Holder and Manufacturer

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

Roche Pharma AG
Emil-Barell-Str. 1,
D-79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
N.V. Roche S.A.
Tél/Tel: +32 (0) 2 525 82 11

България
Рош България ЕООД
Тел: +359 2 818 44 44

Česká republika
Roche s. r. o.
Tel: +420 - 2 20382111

Danmark
Roche a/s
Tlf: +45 - 36 39 99 99

Deutschland
Roche Pharma AG
Tel: +49 (0) 7624 140

Eesti
Roche Eesti OÜ
Tel: + 372 - 6 177 380

Ελλάδα
Roche (Hellas) A.E.
Τηλ: +30 210 61 66 100

España
Roche Farma S.A.
Tel: +34 - 91 324 81 00

France
Roche
Tél: +33 (0) 1 47 61 40 00

Hrvatska
Roche d.o.o
Tel: +385 1 4722 333

Lietuva
UAB “Roche Lietuva”
Tel: +370 5 2546799

Luxembourg/Luxemburg
(Voir/siehe Belgique/Belgien)

Magyarország
Roche (Magyarország) Kft.
Tel: +36 - 23 446 800

Malta
(ara Renju Unit)

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438050

Norge
Roche Norge AS
Tlf: +47 - 22 78 90 00

Österreich
Roche Austria GmbH
Tel: +43 (0) 1 27739

Polska
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

Portugal
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

România
Roche România S.R.L.
Tel: +40 21 206 47 01

Ireland
Roche Products (Ireland) Ltd.
Tel: +353 (0) 1 469 0700

Ísland
Roche a/s
c/o Icepharma hf
Sími: +354 540 8000

Italia
Roche S.p.A.
Tel: +39 - 039 2471

Κύπρος
Γ.Α.Σταμάτης & Σια Λτδ.
Τηλ: +357 - 22 76 62 76

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

Slovenija
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

United Kingdom
Roche Products Ltd.
Tel: +44 (0) 1707 366000

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Your pharmacist may have prepared the medicine for you when you collected your prescription. If not, you can do it easily yourself. See the first set of instructions. **You only need to do this once,** at the beginning of your course.

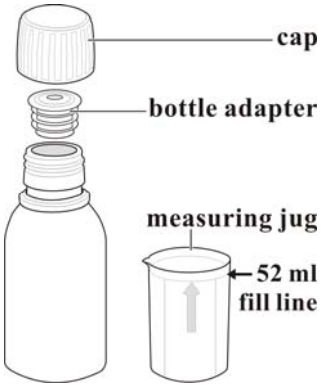
Stage 2 Measure and give the correct dose

Shake the suspension well and draw the appropriate recommended dose into the dispenser. See the second set of instructions. You will need to do this every time you need a dose.

Stage 1: Prepare a new bottle of the medicine

You will need:

- The bottle, containing Tamiflu powder (in the medicine pack)
- The bottle cap (in the medicine pack)
- A plastic measuring jug (in the medicine pack)
- The plastic bottle adapter (in the medicine pack)
- Water



- **Tap the bottle to loosen the powder**
  Tap the closed bottle gently several times to loosen the powder.

- **Use the jug to measure 52 ml of water**
  The measuring jug in the pack has a line marked to show you an exact amount.
  Fill it with water to the indicated level.

- **Add all the water, close and shake**
  Pour all of the water from the jug into the bottle, onto the powder.
  Always use 52 ml of water, whatever the dose you need.
  Put the cap back on the bottle. Shake the bottle well for 15 seconds.

- **Press in the adapter**
  Open the bottle and press the bottle adapter hard into the neck of the bottle.

- **Close the bottle again**
  Screw the cap tightly onto the top of the bottle, which now includes the adapter.
  This will make sure that the bottle adapter fits in the bottle in the right position.

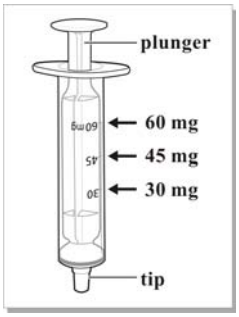
You now have a bottle of Tamiflu oral suspension ready to measure out a dose. You will not need to prepare it again unless you start a new bottle.

Stage 2: Measure and give the correct dose

You will need:

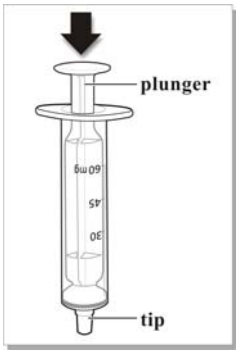
- **A bottle of prepared Tamiflu oral suspension**
- **The oral dispenser from the medicine pack.**

Always use the oral dispenser provided with your medicine to measure a correct dose.
It is marked with three different doses: 30 mg, 45 mg and 60 mg.

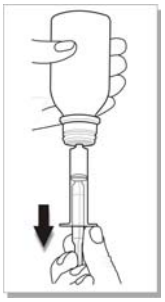


- **Shake the bottle**
  Check the cap is secure, and then shake the bottle of Tamiflu oral suspension.
  Always shake well before use.

- **Prepare the oral dispenser**
  Use the oral dispenser provided in the pack.
  Push the plunger completely down toward the tip of the dispenser.



- **Fill the dispenser with the correct dose**
  Unscrew the cap from the bottle.
  Push the tip of the dispenser into the bottle adapter.
  Then **turn the whole unit upside down** (bottle and dispenser together).



Slowly pull out the plunger to draw medicine into the dispenser.
Stop at the mark that shows the dose you need.
Turn the whole unit upright.
Remove the dispenser from the bottle.

- **Give the medicine into the mouth**
  Deliver the suspension directly into the mouth by pushing down the plunger of the dispenser.
  Make sure the medicine is swallowed.
  You may drink and eat something after taking the medicine.

- **Close the bottle, keep it safe**
  Put the cap back on the bottle. Keep it out of sight and reach of children.

  Store the medicine below 25 º C for up to 10 days. See 5 *How to store Tamiflu*, overleaf.

Take the dispenser apart straight after dosing, and rinse both parts of the dispenser under running tap water.