

SUMMARY OF PRODUCT CHARACTERISTICS

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 and 2.5 mg of sodium benzoate.

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

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

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

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 (or 10 days in immunocompromised patients).

Paediatric population

For infants and children 1 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	Recommended dose for 10 days* Immunocompromised Patients	Amount of oral suspension to withdraw
10 kg to 15 kg	30 mg twice daily	30 mg twice daily	5 ml twice daily
> 15 kg to 23 kg	45 mg twice daily	45 mg twice daily	7.5 ml twice daily
> 23 kg to 40 kg	60 mg twice daily	60 mg twice daily	10 ml twice daily
> 40 kg	75 mg twice daily	75 mg twice daily	12.5 ml twice daily

*The recommended duration in immunocompromised patients (≥ 1 year old) is **10 days**. See *Special Populations, Immunocompromised Patients* for more information.

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

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

The recommended duration in immunocompromised infants (0-12 months old) is **10 days. See *Special Populations, Immunocompromised Patients* for more information.

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	Immunocompromised Patients Recommended dose for 10 days	Amount of oral suspension to withdraw
10 kg to 15 kg	30 mg once daily	30 mg once daily	5 ml once daily
> 15 kg to 23 kg	45 mg once daily	45 mg once daily	7.5 ml once daily
> 23 kg to 40 kg	60 mg once daily	60 mg once daily	10 ml once daily
> 40 kg	75 mg once daily	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 (see Section 5.2 for exposure simulation).

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	Immunocompromised Patients Recommended dose for 10 days	Amount of oral suspension to withdraw	Dispenser size to use
3 kg	9 mg once daily	9 mg once daily	1.5 ml once daily	3 ml
3.5 kg	10.5 mg once daily	10.5 mg once daily	1.8 ml once daily	3 ml
4 kg	12 mg once daily	12 mg once daily	2.0 ml once daily	3 ml
4.5 kg	13.5 mg once daily	13.5 mg once daily	2.3 ml once daily	3 ml
5 kg	15 mg once daily	15 mg once daily	2.5 ml once daily	3 ml
5.5 kg	16.5 mg once daily	16.5 mg once daily	2.8 ml once daily	3 ml
6 kg	18 mg once daily	18 mg once daily	3.0 ml once daily	3 ml
> 6 - 7 kg	21 mg once daily	21 mg once daily	3.5 ml once daily	10 ml
> 7 - 8 kg	24 mg once daily	24 mg once daily	4.0 ml once daily	10 ml
> 8 - 9 kg	27 mg once daily	27 mg once daily	4.5 ml once daily	10 ml
> 9 - 10 kg	30 mg once daily	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 (or up to 12 weeks in immunocompromised patients).

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.

Elderly

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

Immunocompromised patients

Treatment: For treatment of influenza, the recommended duration for immunocompromised patients is 10 days (see sections 4.4, 4.8, 5.1). No dose adjustment is necessary. Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Seasonal prophylaxis: 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).

Excipients

This medicinal product contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

This medicinal product contains sodium benzoate. Sodium benzoate (E211) may increase jaundice in newborn babies (up to 4 weeks old).

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

Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations, including congenital heart defects. A large amount of data on oseltamivir exposure of pregnant women from post-marketing reports and observational studies (more than 1000 exposed outcomes during the first trimester) indicate no malformative nor fetoneonatal toxicity by oseltamivir.

However, in one observational study, while the overall malformation risk was not increased, the results for major congenital heart defects diagnosed within 12 months of birth were not conclusive. In this study, the rate of major congenital heart defects following oseltamivir exposure during the first trimester was 1.76% (7 infants out of 397 pregnancies) compared to 1.01% in unexposed pregnancies from the general population (Odds Ratio 1.75, 95% Confidence Interval 0.51 to 5.98). The clinical significance of this finding is

not clear, as the study had limited power. Additionally, this study was too small to reliably assess individual types of major malformations; moreover women exposed to oseltamivir and women unexposed could not be made fully comparable, in particular whether or not they had influenza.

Animal studies do not indicate reproductive toxicity (see section 5.3).

The use of Tamiflu may be considered during pregnancy if necessary and after considering the available safety and benefit information (for data on benefit in pregnant women please refer to section 5.1 “Treatment of influenza in pregnant women”), and the pathogenicity of the circulating influenza virus strain.

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, 245 immunocompromised patients (including 7 adolescents and 39 children) received Tamiflu for the treatment of influenza and 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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
Skin and			Eczema,	Angioneurotic

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	Common	Uncommon	Rare
subcutaneous tissue disorders			Dermatitis, Rash, Urticaria	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, diarrhoea 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

The treatment of influenza in immunocompromised patients were evaluated in two studies receiving standard dose or high dose regimens (double dose or triple dose) of Tamiflu (see section 5.1). The safety profile of Tamiflu observed in these studies was consistent with that observed in previous clinical trials where Tamiflu was administered for treatment of influenza in non-immunocompromised patients across all age groups (otherwise healthy patients or “at risk” patients [i.e., those with respiratory and/or cardiac co-morbidities]). The most frequent adverse reaction reported in immunocompromised children was vomiting (28%).

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 (see details below).

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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 pregnant women: No controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, however, there is evidence from post-marketing and retrospective observational studies showing benefit of the current dosing regimen in this patient population in terms of lower morbidity/mortality. Results from pharmacokinetic analyses indicate a lower exposure to the active metabolite, however dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section 5.2, Pharmacokinetics, Special Population).

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) FEV₁ 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.

Treatment of influenza in immunocompromised patients: A randomized, double blind study, to evaluate safety and characterize the effects of oseltamivir on the development of resistant influenza virus (primary analysis) in influenza-infected immunocompromised patients, included 151 adult patients, 7 adolescents and 9 children evaluable for efficacy of oseltamivir (secondary analysis, not powered). The study included solid organ transplant [SOT] patients, haematopoietic stem cell transplant [HSCT] patients, HIV positive patients with a CD4+ cell count <500 cells/mm³, patients on systemic immunosuppressive therapy, and those with haematological malignancy. These patients were randomized to be treated, within 96 hours of symptoms onset for a duration of 10 days. The treatment regimens were: standard dose (75mg or weight-adjusted dose for children) twice daily (73 adult patients, 4 adolescent patients and 4 children) or double dose (150mg or weight-adjusted dose for children) twice daily (78 adult patients, 3 adolescent patients and 5 children) of oseltamivir.

The median time to resolution of symptoms (TTRS) for adults and adolescents was similar between the standard dose group (103.4 hours [95% CI 75.4-122.7]) and double dose group (107.2 hours [95% CI 63.9-140.0]). The TTRS for children was variable and the interpretation is limited by the small sample size. The proportion of adult patients with secondary infections in the standard dose group and double dose group was comparable (8.2% vs 5.1%). For adolescents and children, only one patient (an adolescent) in the standard dose group experienced a secondary infection (bacterial sinusitis).

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

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.

Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic:

Prevention during an influenza pandemic has not been studied in controlled clinical studies in children 0-12 months of age. See Section 5.2 for exposure simulation details.

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

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

The incidence of oseltamivir-resistance observed in immunocompromised children (≤ 12 years of age) treated with Tamiflu across the two studies and evaluated for resistance was 20.7% (6/29). Of the six immunocompromised children found with treatment-emergent resistance to oseltamivir, 3 patients

received standard dose and 3 patients high dose (double or triple dose). The majority had acute lymphoid leukemia and were ≤ 5 years of age.

Incidence of Oseltamivir Resistance in Clinical Studies

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

* Full genotyping was not performed in all studies.

Prophylaxis of Influenza

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

Clinical and surveillance data: Natural mutations associated with reduced susceptibility to oseltamivir *in vitro* have been detected in influenza A and B viruses isolated from patients without exposure to oseltamivir. 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 naturally occurring resistance associated with the H275Y mutation in seasonal H1N1 strains has been sporadically detected. 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.

Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic: Simulation of once daily dosing of 3mg/kg in infants <1 year shows an exposure in the same range or higher than for once daily dosing of 75 mg in adults. Exposure does not exceed that for treatment of infants < 1 year (3 mg/kg twice daily) and is anticipated to result in a comparable safety profile (see Section 4.8). No clinical studies of prophylaxis in infants aged <1 have been performed.

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.

Elderly

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).

Pregnant Women

A pooled population pharmacokinetic analysis indicates that the Tamiflu dosage regimen described in Section 4.2 Posology and method of administration results in lower exposure (30% on average across all trimesters) to the active metabolite in pregnant women compared to non-pregnant women. The lower predicted exposure however, remains above inhibitory concentrations (IC₉₅ values) and at a therapeutic level for a range of influenza virus strains. In addition, there is evidence from observational studies showing benefit of the current dosing regimen in this patient population. Therefore, dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section 4.6 Fertility, pregnancy and lactation).

Immunocompromised Patients

Population pharmacokinetic analyses indicate that treatment of adult and paediatric (<18 years old) immunocompromised patients with oseltamivir (as described in Section 4.2. Posology and method of administration) results in an increased predicted exposure (from approximately 5% up to 50%) to the active metabolite when compared to non-immunocompromised patients with comparable creatinine clearance. Due to the wide safety margin of the active metabolite, no dose adjustments are required in patients due to their immunocompromised status. However, for immunocompromised patients with renal impairment, doses should be adjusted as outlined in section 4.2. Posology and method of administration.

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

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

4 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

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.

Preparation of oral suspension

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

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Welwyn Garden City
AL7 1TW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL GB 00031/0903

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