

## 1. NAME OF THE MEDICINAL PRODUCT

Tamiflu 12 mg/ml powder for oral suspension.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of powder for oral suspension contains oseltamivir phosphate equivalent to 30 mg of oseltamivir. After reconstitution, each ml of suspension contains 12 mg oseltamivir. One bottle of reconstituted suspension (75 ml) contains 900 mg of active substance (oseltamivir).

A bottle of 30 g Tamiflu powder for oral suspension contains 25.713 g of sorbitol. One dose of 45 mg oseltamivir administered twice daily delivers 2.6 g of sorbitol.

For a 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*

In patients one year of age and older 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. This indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A (see section 5.1).

#### *Prevention of influenza*

- Post-exposure prevention in individuals one 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 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 antivirals for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses and the impact of the disease in different geographical areas and patient populations.

### 4.2 Posology and method of administration

Tamiflu suspension and Tamiflu 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.

Tamiflu is not recommended for use in children less than one year of age due to insufficient data on safety and efficacy (see section 5.3).

#### *Treatment of influenza*

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.

For infants older than 1 year of age and for children 2 to 12 years of age: 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:

<b>Body Weight</b>	<b>Recommended dose for 5 days</b>
≤ 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

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.

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.

#### *Prevention of influenza*

##### 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 older than 1 year of age and for children 2 to 12 years of age: 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:

<b>Body Weight</b>	<b>Recommended dose for 10 days</b>
≤ 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

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.

It is recommended that Tamiflu powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient (see section 6.6).

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.

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.

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 with severe renal impairment. Recommended doses are detailed in the table below.

<b>Creatinine clearance</b>	<b>Recommended dose for treatment</b>
> 30 (ml/min)	75 mg twice daily
> 10 to ≤ 30 (ml/min)	75 mg once daily, or 30 mg suspension twice daily, or 30 mg capsules twice daily
≤ 10 (ml/min)	Not recommended
dialysis patients	Not recommended

Prevention of influenza: Dose adjustment is recommended for adults with severe renal impairment as detailed in the table below.

<b>Creatinine clearance</b>	<b>Recommended dose for prevention</b>
> 30 (ml/min)	75 mg once daily
> 10 to ≤ 30 (ml/min)	75 mg every second day, or 30 mg suspension once daily, or 30 mg capsules once daily
≤ 10 (ml/min)	Not recommended
dialysis patients	Not recommended

*Elderly*

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

*Children*

There is insufficient clinical data available in children with renal impairment to be able to make any dosing recommendation.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

**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.

The safety and efficacy of oseltamivir for the treatment and prevention of influenza in children of less than one year of age have not been established (see section 5.3).

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.

The safety and efficacy of oseltamivir in either treatment or prevention of influenza in immunocompromised patients have not been established.

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).

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.

#### *Severe renal impairment*

Dose adjustment is recommended for both treatment and prevention in adults with severe renal insufficiency. There is insufficient clinical data available in children with renal impairment to be able to make any dosing recommendation (see sections 4.2 and 5.2).

This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

#### **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.

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

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).

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

#### **4.6 Pregnancy and lactation**

There are no adequate data from the use of oseltamivir in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see section 5.3). Oseltamivir should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. It is not known whether oseltamivir or the active metabolite are excreted in human milk. Oseltamivir should be used during breast-feeding only if the potential benefit for the mother justifies the potential risk for the breast-fed infant.

#### 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

The overall safety profile of Tamiflu is based on data from 2107 adult and 1032 paediatric patients treated for influenza, and on data from 2914 adult and 99 paediatric patients receiving Tamiflu for the prophylaxis of influenza in clinical trials.

In adults, the most commonly reported adverse drug reactions (ADRs) were vomiting and nausea in the treatment studies, and nausea and headache in the prevention studies. The majority of these ADRs 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 drug reaction was vomiting.

The ADRs 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  $< 1/1,000$ ), Very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data). ADRs are added to the appropriate category in the tables according to the pooled analysis from clinical trials. Within each frequency grouping ADRs are presented in the order of decreasing seriousness.

##### Treatment and prevention of influenza in adults and adolescents:

#### **Most Frequent Adverse Drug Reactions ( $\geq 1\%$ in the oseltamivir group) in Studies Investigating Tamiflu for Treatment and Prevention of Influenza in Adults and Adolescents or Through Post-Marketing Surveillance**

System Organ Class (SOC) <i>Frequency Category</i> Adverse Drug Reaction	Percentage of Patients Experiencing the ADR			
	Treatment		Prevention	
	Oseltamivir 75 mg bid (n = 1057)	Placebo (n = 1050)	Oseltamivir 75 mg od (n = 1480)	Placebo (n = 1434)
<b>Infections and infestations</b>				
<i>Common:</i>				
Bronchitis	4 %	5 %	1 %	1 %
Bronchitis acute	1 %	1 %	0 %	< 1 %
Upper respiratory tract infections	0 %	0 %	8 %	8 %
<b>Psychiatric disorders</b>				
<i>Uncommon:</i>				
Hallucination <sup>a</sup>	< 1 %	0 %	< 1 %	0 %
<b>Nervous system disorders</b>				
<i>Very Common:</i>				
Headache	2 %	2 %	20 %	18 %
<i>Common:</i>				
Insomnia	1 %	1 %	1 %	1 %
<i>Uncommon:</i>				
Convulsion <sup>a</sup>	< 1 %	0 %	0 %	0 %
<b>Disorders of the ear and labyrinth</b>				
<i>Common:</i>				
Vertigo	1 %	1 %	< 1 %	< 1 %
<b>Respiratory, thoracic and mediastinal disorders</b>				
<i>Common:</i>				
Cough	1 %	1 %	6 %	6 %
Rhinorrhoea	< 1 %	0 %	2 %	1 %

System Organ Class (SOC) <i>Frequency Category</i> Adverse Drug Reaction	Percentage of Patients Experiencing the ADR			
	Treatment		Prevention	
	Oseltamivir 75 mg bid (n = 1057)	Placebo (n = 1050)	Oseltamivir 75 mg od (n = 1480)	Placebo (n = 1434)
<b>Gastrointestinal disorders</b> <i>Very Common:</i> Nausea <sup>b,c</sup> <i>Common:</i> Vomiting <sup>c</sup> Abdominal pain Diarrhoea Dyspepsia	11 %	7 %	8 %	4 %
<b>Skin and subcutaneous tissue disorders</b> <i>Uncommon:</i> Dermatitis <sup>a</sup> Rash <sup>a</sup> Urticaria <sup>a</sup> Eczema <sup>a</sup>	< 1 %	< 1 %	1 %	1 %
<b>General disorders</b> <i>Common:</i> Dizziness Fatigue Pain	2 %	3 %	2 %	2 %
	1 %	1 %	8 %	8 %
	< 1 %	< 1 %	4 %	3 %

<sup>a</sup> These are events identified during post-marketing surveillance. They were also reported in the pooled clinical studies the incidence presented in the table above.

<sup>b</sup> .Subjects who experienced nausea alone; excludes subjects who experienced nausea in association with vomiting.

<sup>c</sup> The difference between the placebo and oseltamivir groups was statistically significant.

#### Treatment and prevention of influenza in children:

The table below shows the most frequently reported ADRs from paediatric clinical trials.

#### **Most Frequent Adverse Drug Reactions (≥ 1 % in the oseltamivir group in the treatment studies and ≥ 10 % in the oseltamivir group in the prophylaxis study) in Children**

System Organ Class (SOC) <i>Frequency Category</i> Adverse Drug Reaction	Percentage of Patients Experiencing the ADR			
	Treatment		Treatment	Prevention <sup>a</sup>
	Oseltamivir 2 mg/kg bid (n = 515)	Placebo (n = 517)	Oseltamivir 30 to 75 mg <sup>b</sup> (n = 158)	Oseltamivir 30 to 75 mg <sup>b</sup> (n = 99)
<b>Infections and infestations</b> <i>Common:</i> Pneumonia Sinusitis Bronchitis Otitis media	2 %	3 %	0 %	0 %
	2 %	3 %	0 %	0 %
	2 %	2 %	2 %	0 %
	9 %	11 %	1 %	2 %
<b>Disorders of the blood and lymphatic system</b> <i>Common:</i> Lymphadenopathy	1 %	2 %	< 1 %	0 %

System Organ Class (SOC) <i>Frequency Category</i> Adverse Drug Reaction	Percentage of Patients Experiencing the ADR			
	Treatment		Treatment	Prevention <sup>a</sup>
	Oseltamivir 2 mg/kg bid (n = 515)	Placebo (n = 517)	Oseltamivir 30 to 75 mg <sup>b</sup> (n = 158)	Oseltamivir 30 to 75 mg <sup>b</sup> (n = 99)
<b>Respiratory, thoracic and mediastinal disorders</b> <i>Common:</i> Asthma (incl. aggravated) Epistaxis	4 % 3 %	4 % 3 %	0 % 1 %	1 % 1 %
<b>Gastrointestinal disorder</b> <i>Very Common:</i> Vomiting Diarrhoea <i>Common:</i> Nausea Abdominal pain	15 % 10 % 3 % 5 %	9 % 11 % 4 % 4 %	20 % 3 % 6 % 2 %	10 % 1 % 4 % 1 %
<b>Disorders of the eye</b> <i>Common:</i> Conjunctivitis	1 %	< 1 %	0 %	0 %
<b>Disorders of the ear and labyrinth</b> <i>Common:</i> Ear disorder <sup>c</sup> Tympanic membrane disorder	2 % 1 %	1 % 1 %	0 % 0 %	0 % 0 %
<b>Skin and subcutaneous tissue disorders</b> <i>Common:</i> Dermatitis	1 %	2 %	< 1 %	0 %

<sup>a</sup> The prevention study did not contain a placebo arm, i.e. was an uncontrolled study.

<sup>b</sup> Unit dose = weight-based dosing (see section 4.2).

<sup>c</sup> Patients experienced ear ache and ear pain.

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

Further post marketing surveillance data on selected serious adverse drug reactions:

*Immune system disorders*

Frequency not known: hypersensitivity reactions, including anaphylactic/anaphylactoid reactions.

*Psychiatric disorders and nervous system disorders*

Frequency not known: 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 accidental injury or fatal outcomes. These events were reported primarily among pediatric 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.

*Eye disorders*

Frequency not known: visual disturbance.

#### *Cardiac disorders*

Frequency not known: cardiac arrhythmia.

#### *Gastrointestinal disorders*

Frequency not known: gastrointestinal bleedings and hemorrhagic colitis.

#### *Hepato-biliary disorders*

Frequency not known: hepato-biliary system disorders, including hepatitis and elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.

#### *Skin and subcutaneous tissue disorders*

Frequency not known: severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and angioneurotic oedema.

#### Additional information on special populations:

There were no clinically relevant differences in the safety population of the elderly subjects who received oseltamivir or placebo compared with the adult population aged up to 65 years.

The adverse event profile in adolescents and patients with chronic cardiac and/or respiratory disease was qualitatively similar to those of healthy young adults.

### **4.9 Overdose**

There is no experience with overdose. However, the anticipated manifestations of acute overdose would be nausea, with or without accompanying vomiting, and dizziness. Patients should discontinue the treatment in the event of overdose. No specific antidote is known.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antiviral 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 IC<sub>50</sub> 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 IC<sub>50</sub> values for influenza B, up to a median of 8.5 nM, have been observed in published trials.

#### *Reduced sensitivity of viral neuraminidase*

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.

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	4/1245 (0.32%)	5/1245 (0.4%)
Children (1-12 years)	19/464 (4.1%)	25/464 (5.4%)

\* Full genotyping was not performed in all studies.

The rate of emergence of resistance may be higher in the youngest age groups, and in immunosuppressed patients. Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivir-resistant laboratory strains of influenza viruses have been found to contain mutations in N1 and N2 neuraminidases. Resistance mutations tend to be viral sub-type specific (including those found in H5N1 variants).

Naturally occurring mutations in influenza A/H1N1 virus associated with reduced susceptibility to oseltamivir *in vitro* have been detected in patients who, based on the reported information, have not been exposed to oseltamivir. The extent of reduction in susceptibility to oseltamivir and the prevalence of such viruses appears to vary seasonally and geographically.

#### *Treatment of influenza infection*

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 proportional 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 elderly 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  $\geq 37.8$  °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 = 2413) 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 % (135/1063) in the placebo group to 8.6 % (116/1350) in the oseltamivir treated population ( $p = 0.0012$ ).

Treatment of influenza in high risk populations: The median duration of influenza illness in elderly subjects ( $\geq 65$  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 the influenza-positive elderly, 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 ( $\geq 37.8$  °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 duration of 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<sub>1</sub> had increased by 10.8 % in the oseltamivir treated group compared to 4.7 % on placebo ( $p = 0.0148$ ) in this population.

*Treatment of influenza 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 ( $\geq 37.8$  °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 elderly residents of 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).

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

## 5.2 Pharmacokinetic properties

### *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 %).

### *Metabolism*

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.

### *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).

### *Elderly*

Exposure to the active metabolite at steady state was 25 to 35 % higher in elderly (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in the elderly were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for elderly patients unless there is evidence of severe renal impairment (creatinine clearance below 30 ml/min) (see section 4.2).

### *Children*

The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in children aged 1 to 16 years. Multiple-dose pharmacokinetics were studied in a small number of children 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 over 12 years of age are similar to those in adults.

## **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 1500 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 1500 mg/kg/day demonstrated no adverse effects on either sex. In pre- and post-natal rat studies, prolonged parturition was noted at 1500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20 % of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. It is not known whether oseltamivir or the active metabolite is excreted in human milk, but 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 ingredient showed erythema after challenging the induced animals. Reversible irritancy of rabbits' eyes was detected.

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

*Powder for oral suspension:*

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 for powder for oral suspension.

### **6.4 Special precautions for storage**

Powder: Do not store above 30°C.

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

### **6.5 Nature and contents of container**

Carton containing a 100 ml amber glass bottle (with child-resistant plastic screw cap) with 30 g of powder for oral suspension, a plastic adapter, a plastic oral dispenser and a plastic measuring cup. 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.

### **6.6 Special precautions for disposal and other handling**

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

#### **Preparation of Oral Suspension**

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**

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**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  
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**10.    DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>.