

1. NAME OF THE MEDICINAL PRODUCT

Oseltamivir Capsules 75 mg *

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Hard capsule

White to off-white free flowing powder filled in size “2” capsules having white body spin printed with “75mg” and yellow colour cap. Imprints are black.

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 Oseltamivir Capsules 75 mg 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.

Oseltamivir Capsules 75 mg 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

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.

* Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Children weighing > 40 kg, who are able to swallow capsules, may receive treatment with the adult dosage of 75 mg capsules twice daily for 5 days.

Children 1 year of age or older, weighing ≤ 40 kg: In normal situations this product should not be used in children weighing 40 kg or less, since appropriate dose adjustments can only be made by preparation of an extemporaneous formulation and – along with this- an increased risk of dosing errors and a waste of drug (see paragraph on “Extemporaneous formulation” below). If available, for these patients another formulation should be used, e.g. a tablet containing less oseltamivir or an oral suspension. The usual dose for treatment of influenza in children depends on the body weight of the child (see table 1 below).

Children < 1 year of age: Data on the use of oseltamivir in children less than one year of age are scarce (see section 5.3). Therefore, use of Oseltamivir Capsules 75 mg in these patients is not recommended.

Prevention of influenza

Post-exposure prevention

Intake of Oseltamivir Capsules 75 mg should begin as soon as possible within two days of exposure to an infected individual.

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.

Children 1 year of age or older, weighing > 40 kg and who are able to swallow capsules may receive prevention with a 75 mg capsule once daily for 10 days.

Children weighing ≤ 40 kg: In normal situations this product should not be used in children weighing 40 kg or less, since appropriate dose adjustments can only be made by preparation of an extemporaneous formulation and – along with this- an increased risk of dosing errors and a waste of drug (see paragraph on “Extemporaneous formulation” below). If available, another formulation should be used, e.g. a tablet containing less oseltamivir or an oral suspension. The usual dose for prevention of influenza in children depends on the body weight of the child (see table 2 below).

Children < 1 year of age: Data on the use of oseltamivir in children less than one year of age are very scarce (see section 5.3). Therefore, the use of Oseltamivir Capsules 75 mg in this age group is not recommended

Prevention during an influenza epidemic in the community

The recommended dose for prevention of influenza during a community outbreak is the same as for post-exposure prophylaxis, but may be taken for up to 6 weeks.

Extemporaneous formulation:

In situations when commercially manufactured oseltamivir oral suspension or oseltamivir capsules containing less substance is not readily available, adults, adolescents or children who are unable to swallow capsules may receive appropriate doses of oseltamivir by following these instructions:

For patients weighing ≥ 40 kg: The capsule should be opened over a small bowl and the powder should be poured into the bowl. One teaspoon of a sweetened food product such as regular or sugar-free chocolate syrup, honey (only for children two years or older), light brown or table sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce or yogurt should be added to mask the bitter taste. The mixture should be stirred and the entire contents given to the patient. The mixture must be swallowed immediately after its preparation. If there is some mixture left inside the bowl, it should be rinsed with a small amount of water and the patient should drink this remaining mixture.

Children weighing ≤ 40 kg: For allowing proper dosing a **graduated 5 ml syringe** is required as a dosing device. The 75 mg capsule should be opened over a small bowl and the powder should be poured into the bowl. Using the syringe, 5 ml of water should be added to it and the mixture should be stirred for about two minutes. The correct amount of mixture to be drawn up is based upon the patient's weight (see table below).

It is not necessary to draw up any undissolved white powder as this is inert material.

Table 1: Dose recommendation for treatment of influenza

Body Weight	Recommended dose for 5 days	Amount of Oseltamivir Capsules 75 mg mixture for one dose
Less than or equal to 15 kg	30 mg twice daily	2 ml
More than 15 kg and up to 23 kg	45 mg twice daily	3 ml
More than 23 kg and up to 40 kg	60 mg twice daily	4 ml

Table 2: Dose recommendation for prevention of influenza

Body Weight	Recommended dose for 10 days	Amount of Oseltamivir Capsules 75 mg mixture for one dose
Less than or equal to 15 kg	30 mg once daily	2 ml
More than 15 kg and up to 23 kg	45 mg once daily	3 ml
More than 23 kg and up to 40 kg	60 mg once daily	4 ml

The entire content of the syringe should be emptied into another bowl and any unused suspension should be discarded.

One teaspoon of sweetened food product such as regular or sugar-free chocolate syrup, honey (only for children two years or older), light brown or table sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce or yogurt to mask the bitter taste should be added to the mixture and should be stirred. The entire contents should be given to the patient immediately after its preparation. If there is some mixture left inside the bowl, it should be rinsed with a small amount of water and the patient should drink this remaining mixture.

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

Dose adjustment is recommended for adults with severe renal impairment.

Recommended doses are detailed in the table below.

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

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

Elderly

No dose adjustment is required, unless there is evidence of severe renal impairment (see above).

Pandemic situations

In pandemic situations special recommendations may apply. It is therefore suggested to refer to information from local National Authorities or other regulatory bodies, e.g. EMEA (<http://www.emea.europa.eu/>) or USFDA (<http://www.fda.gov/>).

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 fully established (see section 4.2).

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.

The 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).

Oseltamivir Capsules 75 mg is not a substitute for influenza vaccination. Use of Oseltamivir Capsules 75 mg must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as Oseltamivir Capsules 75 mg is administered. Oseltamivir Capsules 75 mg 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).

4.5 Interaction with other medicinal products and other forms of interaction

The 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

Oseltamivir Capsules 75 mg has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The overall safety profile of Oseltamivir Capsules 75 mg 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 oseltamivir capsules 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 oseltamivir 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)
Infections and infestations				
<i>Common:</i>				
Bronchitis	4 %	5 %	1 %	1 %
Bronchitis acute	1 %	1 %	0 %	< 1 %
Upper respiratory tract infections	0 %	0 %	8 %	8 %
Psychiatric disorders				
<i>Uncommon:</i>				
Hallucination ^a	< 1 %	0 %	< 1 %	0 %
Nervous system disorders:				
<i>Very Common:</i>				
Headache	2 %	2 %	20 %	18 %
<i>Common:</i>				
Insomnia	1 %	1 %	1 %	1 %
<i>Uncommon:</i>				
Convulsion ^a	< 1 %	0 %	0 %	0 %
Disorders of the ear and labyrinth				
<i>Common:</i>				
Vertigo	1 %	1 %	< 1 %	< 1 %
Respiratory, thoracic and mediastinal disorders				
<i>Common:</i>				
Cough	1 %	1 %	6 %	6 %
Rhinorrhoea	< 1 %	0 %	2 %	1 %
Gastrointestinal disorders				
<i>Very Common:</i>				
Nausea ^{b,c}	11 %	7 %	8 %	4 %
<i>Common:</i>				
Vomiting ^c	8 %	3 %	2 %	1 %
Abdominal pain	2 %	2 %	2 %	2 %
Diarrhoea	6 %	8 %	3 %	3 %
Dyspepsia	1 %	1 %	2 %	2 %
Skin and subcutaneous tissue disorders				
<i>Uncommon:</i>				
Dermatitis ^a	< 1 %	< 1 %	1 %	1 %
Rash ^a	< 1 %	< 1 %	< 1 %	< 1 %
Urticaria ^a	< 1 %	< 1 %	< 1 %	< 1 %
Eczema ^a	< 1 %	0 %	< 1 %	< 1 %
General disorders				
<i>Common:</i>				
Dizziness	2 %	3 %	2 %	2 %
Fatigue	1 %	1 %	8 %	8 %
Pain	< 1 %	< 1 %	4 %	3 %

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

^b Subjects who experienced nausea alone; excludes subjects who experienced nausea in association with vomiting.

^c 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 ($\geq 1\%$ in the oseltamivir group) in studies investigating oseltamivir for treatment and prevention of influenza in children

System Organ Class (SOC) <i>Frequency Category</i> Adverse Drug Reaction	Percentage of Patients Experiencing the ADR			
	Treatment		Treatment	Prevention ^a
	Oseltamivir 2 mg/kg bid (n = 515)	Placebo (n = 517)	Oseltamivir 30 to 75 mg ^b (n = 158)	Oseltamivir 30 to 75 mg ^b (n = 99)
Infections and infestations				
<i>Common:</i>				
Pneumonia	2 %	3 %	0 %	0 %
Sinusitis	2 %	3 %	0 %	0 %
Bronchitis	2 %	2 %	2 %	0 %
Otitis media	9 %	11 %	1 %	2 %
Disorders of the blood and lymphatic system				
<i>Common:</i>				
Lymphadenopathy	1 %	2 %	< 1 %	0 %
Nervous system disorders:				
<i>Very Common:</i>				
Headache	2 %	2 %	20 %	18 %
<i>Common:</i>				
Insomnia	1 %	1 %	1 %	1 %
<i>Uncommon:</i>				
Convulsion ^a	< 1 %	0 %	0 %	0 %
Respiratory, thoracic and mediastinal disorders				
<i>Common:</i>				
Asthma (incl. aggravated)	4 %	4 %	0 %	1 %
Epistaxis	3 %	3 %	1 %	1 %
Gastrointestinal disorders				
<i>Very Common:</i>				
Vomiting	15 %	9 %	20 %	10 %
Diarrhoea	10 %	11 %	3 %	1 %
<i>Common:</i>				
Nausea	3 %	4 %	6 %	4 %
Abdominal pain	5 %	4 %	2 %	1 %
Disorders of the eye				
<i>Common:</i>				
Conjunctivitis	1 %	< 1 %	0 %	0 %
Disorders of the ear and labyrinth				
<i>Common:</i>				
Ear disorders ^c	2 %	1 %	0 %	0 %
Tympanic membrane disorder	1 %	1 %	0 %	0 %
Skin and subcutaneous tissue disorders				
<i>Common:</i>				
Dermatitis ^a	1 %	2 %	< 1 %	0 %

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

b Unit dose = weight-based dosing (see section 4.2).

c 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 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 oseltamivir, 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 paediatric and adolescent patients and often had an abrupt onset and rapid resolution. The contribution of oseltamivir to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir.

Eye disorders

Frequency not known: visual disturbance.

Cardiac disorders

Frequency not known: cardiac arrhythmia.

Gastrointestinal disorders

Frequency not known: gastrointestinal bleedings and haemorrhagic 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 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 trials.

Reduced sensitivity of viral neuraminidase

There has been no evidence for emergence of drug resistance associated with the use of oseltamivir 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 clinical studies sponsored by the innovator's manufacturer. 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.

For further information on latest resistance surveillance data see e.g.

<http://www.who.int/csr/disease/influenza/en/index.html>

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 ≥ 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 (≥ 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 (≥ 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.

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

Prevention of influenza

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory-confirmed influenza. The transmissibility 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.

Following single dose administration of Oseltamivir Capsules 75 mg in healthy volunteers, the mean (\pm SD) oseltamivir C_{max} value was 71 ng/ml (\pm 29), respectively and the corresponding value for AUC was 160 ng.h/ml (\pm 36). The median (range) oseltamivir t_{max} value was 0.98 (\pm 0.81) hours.

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 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 the 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 Oseltamivir Capsules 75 mg 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

Capsule core:

Croscarmellose sodium
pregelatinised starch
sodium stearyl fumarate
talc.

Capsule shell:

Gelatin
iron oxide yellow
titanium dioxide

Printing ink:

Shellac
black iron oxide
propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

- White, induction-sealed, 50 ml HDPE bottles fitted with child-resistant closures and containing a silica gel bag desiccant. The HDPE bottles are kept in a carton box. Pack size: 30 capsules.
- Carton box containing 10 capsules in a blister pack (clear PVC/PE/PVDC film, sealed with aluminium foil).

6.6 Special precautions for disposal

No special requirements.

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

7. SUPPLIER

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References:

European Public Assessment Report (EPAR) on Tamiflu:

<http://www.emea.europa.eu/humandocs/Humans/EPAR/tamiflu/tamiflu.htm>

Follow-up recommendations from CHMP on Novel Influenza (H1N1) outbreak, Tamiflu (oseltamivir), Relenza (zanamivir), EMEA/H/A-5.3/1172, Article 5(3) of Regulation (EC) No 726/2004:

<http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/32609509en.pdf>

Influenza (Flu) Antiviral Drugs and Related Information:

<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm100228.htm>