SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oseltamivir (as phosphate) Capsules 75 mg*

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains oseltamivir phosphate equivalent to 75 mg of oseltamivir.

Each tablet contains a small amount (less than 1 mg) FD&C yellow # 6 (Sunset yellow FCF). For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Hard-shell gelatin capsule with yellow opaque cap and white opaque body imprinted axially with 'MYLAN' over 'OS3' in black ink on both cap and body, filled with white to off-white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Treatment of influenza

In patients one year of age and older 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).

Oseltamivir (as phosphate) Capsules 75 mg is indicated for the treatment of infants less than 1 year of age during a pandemic influenza outbreak (see section 5.2).

The treating physician or health care provider should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure potential benefit to the child.

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.
- Use of Oseltamivir (as phosphate) 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. 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 (as phosphate) Capsules 75 mg 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).

Oseltamivir (as phosphate) 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 on the use of oseltamivir for treatment and prophylaxis should take into consideration the characteristics of the circulating influenza viruses, 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).

It is therefore suggested to refer to information from local National Authorities and from WHO (http://www.who.int/en/).

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

4.2 Posology and method of administration

Adults, adolescents or infants and children (1 year of age or older) who cannot swallow capsules may receive oseltamivr suspension.

Adults, and adolescents aged 13 years and over

Treatment

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

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

Post-exposure prevention

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

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

Prevention during an influenza epidemic in the community

The recommended dose for prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to 6 weeks.

Children aged 1 to 12 years

Treatment

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

Child's body weight	Recommended dose for 5 days
10–15 kg	30 mg twice daily
15–23 kg	45 mg twice daily
23–40 kg	60 mg twice daily
> 40 kg	75 mg twice daily

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

Post-exposure prevention

The recommended post-exposure prevention doses of oseltamivir for infants and children aged 1 year or older are:

Child's body weight	Recommended dose for 10 days
10–15 kg	30 mg once daily
15–23 kg	45 mg once daily
23–40 kg	60 mg once daily
> 40 kg	75 mg once daily

Prevention during an influenza epidemic in the community

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

Infants aged less than 1 year

Treatment

The recommended treatment dose for infants aged below 1 year is between 2 mg/kg twice daily and 3 mg/kg twice daily during a pandemic influenza outbreak. This recommendation is based on limited pharmacokinetic and safety data indicating that in the majority of patients these doses provide plasma drug exposures similar to those shown to be clinically efficacious in older children and adults (see section 5.2).

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

The following age-adjusted dosing regimens are recommended for treatment of infants aged below 1 year:

Infant's age	**Recommended dose for 5 days**
birth–1 month*	2 mg/kg twice daily
1–3 months	2.5 mg/kg twice daily
3–12 months	3 mg/kg twice daily

∗ No data are available on the administration of oseltamivir to infants aged below 1 month

These age-based dosing recommendations are not intended for premature infants, i.e. those with a postmenstrual age below 37 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

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

Special populations

Hepatic impairment

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

Renal impairment

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

Creatinine clearance	**Recommended dose for treatment**
> 60 ml/minute	75 mg twice daily
30–60 ml/minute	30 mg twice daily
10–30 ml/minute	30 mg once daily
≤ 10 ml/minute	Not recommended—no data available
Patients on haemodialysis	30 mg after each haemodialysis session
Patients on peritoneal dialysis*	30 mg single dose

∗ Data from studies on continuous ambulatory peritoneal dialysis (CAPD) patients; the clearance of oseltamivir carboxylate is expected to be higher with automated peritoneal dialysis (APD) mode. Dialysis 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 (aged 13 to 17 years) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for treatment
> 60 ml/minute	75 mg once daily
30–60 ml/minute	30 mg once daily
10–30 ml/minute	30 mg every second day
≤ 10 ml/minute	Not recommended—no data available
Patients on haemodialysis	30 mg every second haemodialysis session
Patients on peritoneal dialysis*	30 mg once weekly

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

Clinical data on infants and children (aged 12 years and younger) with renal impairment are not sufficient to be able to recommend doses.

Older people

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

Immunocompromised patients

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

Method of administration

Oral use.

Adults, adolescents (aged 13 to 17 years) or infants and children (aged 1 year or older) who are unable to swallow capsules may receive oseltamivir suspension.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients (section 6.1).

4.4 Special warnings and precautions for use

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

Oseltamivir is **not** a substitute for influenza vaccination. Use of oseltamivir must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as oseltamivir is administered. Oseltamivir 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 can be highly variable (see section 5.1). Therefore, prescribers should consider the most recent information on susceptibility of the currently circulating viruses to oseltamivir when deciding whether to use oseltamivir.

Severe concomitant condition

No information is available on 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 and respiratory disease

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

Paediatric population

No data allowing a dose recommendation for premature children (< 37 weeks post-menstrual age*) are currently available.

* Time between first day of last normal menstrual period and day of assessment, gestational age plus post-natal age.

Severe renal impairment

Dose adjustment is recommended for both treatment and prevention in adolescents (aged 13 to 17 years) and adults with severe renal impairment. Clinical data on infants and children (aged 1 year or older) with renal impairment are not sufficient to be able to recommend suitable doses (see sections 4.2 and 5.2).

Neuropsychiatric events

Neuropsychiatric events have been reported during oseltamivir treatment in patients with influenza, especially in children and adolescents. These events also occur in patients with influenza who have not been treated with oseltamivir. Patients should be closely monitored for behavioural changes and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8).

4.5 Interactions 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 approximately 2-fold increase in exposure to the active metabolite of oseltamivir.

Amoxicillin

Oseltamivir has no kinetic interaction with amoxicillin, which is eliminated through 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 taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Additional information

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

In rats, oseltamivir and its active metabolite appear in milk. Very limited information is available on children breast-fed by mothers taking oseltamivir and on the presencce of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and its active metabolite were detected in breast milk, however the levels were low, which would result in a subtherapeutic dose to the infant. In the light of 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 oseltamivir affects male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Oseltamivir 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 oseltamivir is based on data from 6049 adults and adolescents and 1473 paediatric patients treated with oseltamivir or placebo for influenza, and on data from 3990 adult and adolescent and 253 paediatric patients receiving oseltamivir or either placebo or no treatment for the prophylaxis of influenza in clinical trials. In addition, 475 immunocompromised patients (including 18 children—10 oseltamivir and 8 placebo) received oseltamivir or placebo for the prophylaxis of influenza.

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

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

(See section 4.4 for neuropsychiatric disorders.)

Tabulated list of adverse reactions

The adverse reactions in the tables below fall into the following categories:

Very common (1 in 10); common (between 1 in 100 and 1 in 10); uncommon (between 1 in 1000 and 1 in 100); rare (between 1 in 10 000 and 1 in 1000); and very rare (fewer than 1 in 10 000). Adverse reactions 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:

Adverse reactions that occurred most frequently at the recommended dose (75 mg twice daily for 5 days for treatment and 75 mg once daily for up to 6 weeks for prophylaxis) in studies on adults and adolescents are shown in Table 1.

The safety profile reported in subjects who received the recommended dose of oseltamivir for prophylaxis (75 mg once daily for up to 6 weeks) was qualitatively similar to that in treatment studies, despite longer duration of dosing in the prophylaxis studies.

Table 1: Adverse reactions in studies investigating oseltamivir 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, rhinorrhoea		
Gastrointestinal disorders	nausea	vomiting, abdominal pain (including upper abdominal pain), dyspepsia		gastrointestinal bleedings, haemorrhagic colitis
Hepatobiliary disorders			elevated liver enzymes	fulminant hepatitis, hepatic failure, hepatitis

System–organ–class (SOC)	Adverse reactions according to frequency			
	Very common	**Common**	**Uncommon**	**Rare**
Skin and subcutaneous tissue disorders			eczema, dermatitis, rash, urticaria	angioedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
General disorders and administration site conditions		pain, dizziness (including 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 and children with asthma aged 6–12 years) participated in clinical studies of oseltamivir given for the treatment of influenza. Of those, 851 children received oseltamivir suspension. A total of 158 children received the recommended dose of oseltamivir 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 oseltamivir for treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg once daily])

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 (including 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 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 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 oseltamivir to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir.

Hepato-biliary disorders

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

Other special populations

Paediatric population (infants aged less than one year)

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 2400 infants of that age), epidemiological databases research and postmarketing reports suggest that the safety profile in infants aged less than one year is similar to the established safety profile of children aged one year and older.

Elderly patients and patients with chronic cardiac and/or respiratory disease

The population included in the influenza treatment studies comprised otherwise healthy adults and adolescents and patients at higher risk of developing complications associated with influenza (e.g. elderly patients and patients with chronic cardiac or respiratory disease). In general, the safety profile in the ‘at-risk’ patients was qualitatively similar to that in otherwise healthy adults and adolescents.

Immunocompromised patients

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

Children with bronchial asthma

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

4.9 Overdose

Reports of overdoses with oseltamivir 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 with therapeutic doses of oseltamivir, described in section 4.8.

No specific antidote is known.

Children

Overdose has been reported more frequently for children than for adults and adolescents. Caution should be exercised when preparing oseltamivir oral suspension and when giving oseltamivir 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. This metabolite selectively inhibits influenza viral neuraminidase enzymes, which are glycoproteins on the virion surface. Viral neuraminidase activity is important both for viral entry into uninfected cells and for the release of virus particles from infected cells, and, thus, for the spread of 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 adults given 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_{50} 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_{50} values for influenza B, up to a median of 8.5 nM, have been observed in published studies.

Clinical studies

Treatment of influenza infection

Oseltamivir is effective against illnesses caused by influenza virus only. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population, which included both influenza-positive and influenza-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 46–74%) 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 or sweating, 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 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 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 1–12 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 6–12 years of whom 53.6% were influenza-positive. In the oseltamivir-treated group, the median duration of illness was not reduced significantly. By day 6 (the last day of treatment) FEV_1 had increased by 10.8% in the oseltamivir-treated group compared to 4.7% on placebo (p = 0.0148) in this population.

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 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 1 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) 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 7 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 ≤ 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 10 days. In the total population, the incidence of laboratory-confirmed clinical influenza was reduced 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, the incidence of influenza was reduced 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 aged 1 to 12 years, 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 2 other studies on 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 for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4%) in the placebo group to 1/276 (0.4%) in the oseltamivir group (92% reduction [95% CI 1.5–6.6; p = 0.0015]). The NNT in this study was 25 (95% CI 23–62).

Prophylaxis of influenza in immunocompromised patients: A double-blind, placebo-controlled, randomised study was conducted for seasonal prophylaxis of influenza in 475 immunocompromised patients (388 patients with solid organ transplantation [195 placebo; 193 oseltamivir], 87 patients with haemopoetic stem cell transplantation [43 placebo; 44 oseltamivir], no patient with other immune-suppressant conditions), including 18 children aged 1–12 years. The primary endpoint in this study was the incidence of laboratory-confirmed clinical influenza as determined by viral culture or a 4-fold rise in HAI antibodies. The incidence of laboratory-confirmed clinical influenza was 2.9% (7/238) in the placebo group and 2.1% (5/237) in the oseltamivir group (95% CI 2.3–4.1%; p = 0.772).

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

Oseltamivir resistance

Clinical studies: The risk of emergence of influenza viruses with reduced susceptibility or frank resistance to oseltamivir has been examined during Roche-sponsored clinical studies. All patients 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*	**Genotyping and phenotyping***
Adults and adolescents	4/1245 (0.32%)	4/1245 (0.4%)
Children (1–12 years)	19/464 (4.1%)	25/464 (5.4%)

∗ Full genotyping was not performed in all studies

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

Clinical and surveillance data: Natural mutations associated with reduced susceptibility to oseltamivir in vitro have been detected in influenza A and B viruses isolated from patients without exposure to oseltamivir. Resistant strains selected during oseltamivir treatment have been isolated from both immunocompetent and immunocompromised patients. Immunocompromised patients and young children are at a higher risk of developing oseltamivir-resistant virus during treatment.

Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivir-resistant laboratory strains of influenza viruses have been found to contain mutations in N1 and N2 neuraminidases. Resistance mutations tend to be viral sub-type specific. Since 2007 resistance associated H275Y mutation in seasonal H1N1 strains has become widespread. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. In 2008, H275Y was found in > 99% of circulating H1N1 influenza isolates in Europe. The 2009 H1N1

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

5.2 Pharmacokinetic properties

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 75-mg capsule from Mylan Laboratories in healthy volunteers, the mean (± SD) oseltamivir C_{max} value was 104 ng/ml (± 39 ng/ml) and the corresponding value for AUC was 206 ng·hour/ml (± 51 ng·hour/ml). The median (± SD) oseltamivir t_{max} value was 0.72 hour (± 0.37 hour).

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 litres/hour) exceeds glomerular filtration rate (7.5 litres/hour) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20% of an oral radiolabelled dose is eliminated in faeces.

Special populations

Children

Infants aged less than 1 year: Limited pharmacokinetic and safety data are available for infants aged less than 1 year. Results from pharmacokinetic modelling based on these data in addition to data from studies in adults and infants and children 1 year of age or older demonstrate that doses of 3 mg/kg twice daily for infants aged 3–12 months and 2.5 mg/kg twice daily for infants aged between 1–3 months provide exposures similar to those shown to be clinically efficacious in adults and infants and children aged 1 year or older (see sections 4.1 and 4.2). There are currently no data in infants less than 1 month of age using oseltamivir.

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

pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older are similar to those in adults.

Older people

Exposure to the active metabolite at steady state was 25–35% higher in elderly (age 65–78 years) compared to adults younger than 65 years of age given comparable doses of oseltamivir. Half-lives in the elderly were similar to those in young adults. On the basis of drug exposure and tolerability, dosage adjustment is not required for elderly patients unless there is evidence of moderate or severe renal impairment (creatinine clearance less than 60 ml/minute).

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.

Hepatic impairment

In vitro studies have concluded that exposure to oseltamivir is not expected to increase significantly nor is exposure to the active metabolite expected to significantly decrease in patients with hepatic impairment.

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 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 human use, these findings do not change the benefit–risk balance of oseltamivir for the recommended therapeutic indications.

Teratology studies have been conducted in rats and rabbits at doses of up to 1.5 g/kg daily and 500 mg/kg daily, respectively. No effects on fetal development were observed. A rat fertility study up to a dose of 1.5 g/kg daily demonstrated no adverse reactions on either sex. In pre- and post-natal rat studies, prolonged parturition was noted at 1.5 g/kg daily: the safety margin between human exposure and the highest no-effect dose (500 mg/kg daily) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Fetal exposure in rats and rabbits was approximately 15–20% of that of the mother.

In lactating rats, oseltamivir and the active metabolite are present in milk. Limited data indicate that oseltamivir and its 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 (1.31 g/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 daily given from 7 to 21 days postpartum).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Capsule core:

Croscarmellose sodium
Povidone Pregelatinised
starch Sodium stearyl
fumarate Talc

Capsule shell:

D&C yellow #10 (E104)
FD&C yellow # 6 (Sunset yellow FCF, E110)
Gelatin
Titanium dioxide (E171)

Printing ink:

Black iron oxide (E172)
Potassium hydroxide
Propylene glycol
Shellac

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

HDPE bottle pack and Triplex blister pack: 24 months

PVC blister pack: 18 months

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container.

6.5 Nature and contents of container

HDPE bottle pack

Round wide mouth white HDPE bottle with white opaque polypropylene screw cap. 30 capsules per bottle.

PVC blister pack

Clear transparent PVC-Al blisters. 10 capsules per card.

Triplex blister pack

Clear transparent, PVC/PE/PVDC-Al blisters. 10 capsules per card.

6.6 Special precautions for disposal

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

Home preparation

When commercially manufactured oseltamivir oral liquid is not available, patients who are unable to swallow capsules may receive appropriate doses of oseltamivir prepared at home.

When appropriate capsule strengths are available for the dose needed, the dose is given by opening the capsule and mixing its contents with no more than one teaspoon of a suitable

sweetened food product. The bitter taste can be masked by products such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce). The mixture should be stirred and all of it given to the patient. The mixture must be swallowed immediately after its preparation.

When only 75-mg capsules are available, and smaller doses are needed, the preparation of oseltamivir suspension involves additional steps. Detailed instructions can be found in the package leaflet under 'Making oseltamivir suspension at home'.

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Reference list

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