Oseltamivir phosphate 30/45/75

Seltavir 30/45/75

Name of the medicinal product

(Oseltamivir Phosphate 30 mg Hard Capsules)
(Oseltamivir Phosphate 45 mg Hard Capsules)
(Oseltamivir Phosphate 75 mg Hard Capsules)

QUALITATIVE AND QUANTITATIVE COMPOSITION

30 mg capsules, containing 39.4 mg oseltamivir phosphate equivalent to 30 mg of oseltamivir.
45 mg capsules, containing 59.1 mg oseltamivir phosphate equivalent to 45 mg of oseltamivir.
75 mg capsules, containing 98.5 mg oseltamivir phosphate equivalent to 75 mg of oseltamivir.

Pharmaceutical form

Hard Capsules

Description:

Oseltamivir Phosphate 30 mg Hard Capsules

Size "4" hard gelatin capsules with light yellow opaque colour body with black colour band,imprinted with "M" and light yellow opaque colour cap imprinted with "30 mg".

Oseltamivir Phosphate 45 mg Hard Capsules

Size "4" hard gelatin capsules with grey opaque colour body with black colour band,imprinted with "M" and grey opaque colour cap imprinted with "45 mg".

Oseltamivir Phosphate 75 mg Hard Capsules

Size "2" hard gelatin capsules with grey opaque colour body with black colour band,imprinted with "M" and light yellow opaque colour cap imprinted with "75 mg"

CLINICAL PARTICULARS

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 Pharmacodynamic properties).

Based on limited pharmacokinetic and safety data, Oseltamivir Capsules can be used in children 6 to 12 months of age for treatment during a pandemic influenza outbreak. The treating physician should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to ensure there is a potential benefit to the child

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 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 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.

Posology and method of administration

75 mg doses can be administered as either
- one 75 mg capsule or
- one 30 mg capsule plus one 45 mg capsule

During situations when commercially manufactured Oseltamivir Capsules oral suspension is not readily available, adults, adolescents or children who are unable to swallow capsules may receive appropriatedoses of Oseltamivir Capsules by opening capsules and pouring the contents of capsules into a suitable, small amount (1 teaspoonmaximum) 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. The mixture should be stirred and the entire contents given to the patient. The mixture must be swallowed immediately after its preparation.

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 Oseltamivir Capsules is indicated in the table below.

The following weight-adjusted dosing regimens are recommended

Body Weight	Recommended dose for 5 days
≤ 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 children 6 to 12 months of age: Depending on the pathogenicity of the circulating influenza virus strain, children between 6 and 12 months of age can be treated with Oseltamivir Capsules during a pandemic influenza outbreak, although the available data are limited. Pharmacokinetic data indicate that a dosage of 3 mg/kg twice daily in children 6 to 12 months of age provides plasma drug exposures in the majority of patients similar to those shown to be clinically efficacious in children age one or older and adults (see section Pharmacokinetic properties).The recommended dose for treatment of children 6 to 12 months of age is 3 mg per kg body weight twice daily for 5 days for treatment.

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: The recommended post-exposure prevention dose of Oseltamivir Capsules is:

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

Prevention during an influenza epidemic in the community

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

Infants 6-12 months of age

This procedure describes the preparation of a 10 mg/ml solution that will provide one patient with enough medication for a 5-day course of treatment or a 10-day course of prophylaxis. The pharmacist may compound a suspension (10 mg/ml) from Oseltamivir Capsules 30 mg, 45 mg or 75 mg capsules using water containing 0.1% w/v sodium benzoate added as a preservative. First, calculate the Total Volume needed to be compounded and dispensed for each patient. The Total Volume required is determined by the weight of the patient according to the recommendation in the table below:

Volume of Compounded Suspension (10 mg/ml) Prepared Based Upon the Patient's Weight

Body Weight (kg)	Total Volume to Compound per Patient Weight (ml)
≤ 7 kg	30 ml
7 to 12 kg	45 ml

Second, determine the number of capsules and the amount of vehicle (water containing 0.1% w/v sodium benzoate added as a preservative) that is needed to prepare the Total Volume (calculated from the table above: 30 ml, 45 ml) of compounded suspension (10 mg/ml) as shown in the table below:

Number of Capsules and Amount of Vehicle Needed to Prepare the Total Volume of a Compounded Suspension (10 mg/ml) :

Total Volume of Compounded Suspension to be Prepared	Required Number of Oseltamivir Capsules(mg of oseltamivir)			Required Volume of Vehicle
	75 mg	45 mg	30 mg	
30 ml	4 capsules (300mg)	Please use alternative capsule strength	10 capsules (300 mg)	29.5 ml
45 ml	6 capsules (450mg)	10 capsules (450 mg)	15 capsules (450 mg)	44 ml

* No integral number of capsules can be used to achieve the target concentration; therefore, please use either the 30 mg or 75 mg capsules.

Third, follow the procedure below for compounding the suspension (10 mg/ml) from Oseltamivir Capsules :

1. Carefully separate the capsule body and cap and transfer the contents of the required number of Oseltamivir Capsules into a clean mortar.
2. Triturate the granules to a fine powder.
3. Add one-third (1/3) of the specified amount of vehicle and triturate the powder until a uniform suspension is achieved.
4. Transfer the suspension to an amber glass or amber polyethyleneterephthalate (PET) bottle. A funnel may be used to eliminate any spillage.
5. Add another one-third (1/3) of the vehicle to the mortar, rinse the pestle and mortar by a triturating motion and transfer the vehicle into the bottle.
6. Repeat the rinsing (Step 5) with the remainder of the vehicle.
7. Close the bottle using a child-resistant cap.
8. Shake well to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension. (Note: Undissolved residue may be visible but is comprised of inert ingredients of Oseltamivir Capsules, which are insoluble. However, the active drug, oseltamivir phosphate, readily dissolves in the specified vehicle and therefore forms a uniform solution.) 9. Put an ancillary label on the bottle indicating "Shake Gently Before Use".
10. Instruct the parent or caregiver that after the patient has completed the full course of therapy any remaining solution must be discarded. It is recommended that this information be provided by affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
11. Place an appropriate expiration date label according to storage condition (see below). Storage of the pharmacy-compounded suspension (10 mg/ml) Room temperature storage conditions: Stable for 3 weeks (21 days) when stored at room temperature "do not store above 25 °C". Refrigerated storage conditions: Stable for 6 weeks when stored at 2 °C - 8 °C.

Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, use by date, drug name and any other required information to be in compliance with local pharmacy regulations.

Refer to the table below for the proper dosing instructions.

Dosing Chart for Pharmacy-Compounded Suspension (10 mg/ml) from Oseltamivir Capsules for Infants 6 – 12 Months of Age

Body Weight (rounded to the nearest 0.5 kg)	Treatment Dose (for 5 days)
6 kg	1.50 ml twice daily
7 kg	2.10 ml twice daily
8 kg	2.40 ml twice daily
9 kg	2.70 ml twice daily
≥ 10 kg	3.00 ml twice daily

Note: This compounding procedure results in a 10 mg/ml suspension.

Dispense the suspension with a graduated oral syringe for measuring small amounts of suspension.

If possible, mark or highlight the graduation corresponding to the appropriate dose on the oral syringe for each patient. The appropriate dose must be mixed by the caregiver with an equal quantity of sweet liquid food, such as sugar water, chocolate syrup, cherry syrup, dessert toppings (like caramel or fudge sauce) to mask the bitter taste.

Special populations

Hepatic impairment

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

Renal impairment

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

Creatinine clearance	Recommended dose for treatment
> 60 (ml/min)	75 mg twice daily
> 30 to ≤ 60 (ml/min)	30 mg twice daily
> 10 to ≤ 30 (ml/min)	30 mg once daily
≤ 10 (ml/min)	Not recommended
Hemodialysis patients	30 mg after each hemodialysis session
Peritoneal dialysis patients*	30 mg single dose

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

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

Creatinine clearance	Recommended dose for prophylaxis
> 60 (ml/min)	75 mg once daily
> 30 to ≤ 60 (ml/min)	30 mg once daily
> 10 to ≤ 30 (ml/min)	30 mg every second day
≤ 10 (ml/min)	Not recommended
Hemodialysis patients	30 mg after each second hemodialysis session
Peritoneal dialysis patients*	30 mg once weekly

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

Geriatric Use

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

Contraindications

Oseltamivir Capsules is contraindicated in patients with known hypersensitivity to Oseltamivir phosphate or to any component of the product.

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. 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 Pharmacodynamic properties).

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 Oseltamivir Capsules, 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 Oseltamivir Capsules to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking Oseltamivir Capsules. Three separate large epidemiological studies confirmed that influenza infected patients receiving Oseltamivir Capsules are at no higher risk to develop neuropsychiatric events in comparison to influenza infected patients not receiving antivirals. Patients with influenza should be closely monitored for signs of abnormal behaviour. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

Oseltamivir Capsules is not a substitute for influenza vaccination. Use of Oseltamivir Capsules must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as Oseltamivir Capsules is administered. Oseltamivir Capsules 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 Posology and method of administration and Pharmacokinetic properties).

Females & Males of Reproductive Potential

Fertility

Fertility studies have been conducted in rats. There was no evidence of an effect on male or female fertility at any dose of oseltamivir studied.

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 Pharmacokinetic properties), 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), warfarin, rimantadine or amantadine

Pregnancy and lactation

Risks to the Developing Embryo/Fetus and to the Mother

In animal reproductive studies in rats and rabbits, no teratogenic effect was observed. Foetal exposure in rats and rabbits was approximately 15-20% of that of the mother. No controlled clinical trials have been conducted on the use of oseltamivir in pregnant women; however there is evidence from post-marketing and observational studies showing benefit of the current dosing regimen in this patient population. Results from pharmacokinetic analyses indicate a lower exposure to the active metabolite, however dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza. A large amount of data from pregnant women exposed to Oseltamivir (more than 1000 exposed outcomes during the first trimester) from post-marketing reports and observational studies in conjunction with animal studies indicate no direct or indirect harmful effects with respect to pregnancy, embryonal/foetal or postnatal development (see Nonclinical safety data Preclinical safety data). Pregnant women may receive Oseltamivir Capsules, after considering the available safety and benefit information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the pregnant woman.

Lactation

In lactating rats, oseltamivir and the active metabolite are excreted in milk. Very limited information is available on children breast-fed by mothers taking oseltamivir and on excretion of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and the active metabolite were detected in breast milk, however the levels were low, which would result in a subtherapeutic dose to the infant. Based on this information, the pathogenicity of the circulating influenza virus strain and the underlying condition of the lactating woman, administration of oseltamivir may be considered, where there are clear potential benefits to lactating mothers

Labor and Delivery

The safe use of oseltamivir during labor and delivery has not been established.

Effects on ability to drive and use machines

No or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of Safety Profile

The overall safety profile of Oseltamivir Capsules is based on data from 2646 adult/adolescent and 859 paediatric patients with influenza, and on data from 1943 adult/adolescent and 148 paediatric patients receiving Oseltamivir Capsules for the prophylaxis of influenza in clinical trials. In adults/adolescent, the most commonly reported adverse drug reactions (ADRs) were vomiting, nausea and headache in the treatment 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 adult/adolescent prophylaxis studies, the most frequently reported ADRs were nausea, vomiting, headache and pain. In children, the most commonly reported ADR was vomiting. In the majority of patients, these events did not lead to discontinuation of Oseltamivir Capsules.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials are listed according to the MedDRA system organ class. The corresponding frequency category for each adverse drug reaction listed in the tables below is based on the following convention: Very Common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000).

Treatment and prevention of influenza in adults and adolescents:

In adult/adolescent treatment and prophylaxis studies, ADRs that occurred the most frequently (≥ 1%) at the recommended dose (75 mg b.i.d. for 5 days for treatment and 75 mg o.d. for up to 6 weeks for prophylaxis), and whose incidence is at least 1% higher on Oseltamivir Capsules compared to placebo are presented in the table below.

The population included in the influenza treatment studies comprised of otherwise healthy adults/adolescents and patients "at risk" (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 patients "at risk" was qualitatively similar to that in otherwisehealthy adults/adolescents.

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

Summary of Adverse Drug Reactions in ≥ 1 % of adult and adolescent patients that received oseltamivir for treatment or prophylaxis of influenza, in clinical studies (difference to placebo ≥ 1 %)

System Organ Class (SOC) Adverse Drug Reaction	Treatment studies	Prophylaxis	Frequency Category[a]
	Oseltamivir 75 mg bid (n = 2646)	Oseltamivir 75 mg od (n = 1943)	
Nervous system disordersHeadache	2 %	17 %	very common
Gastrointestinal disordersNauseaVomitig	10% 8%	8% 2%	very common common
General disordersPain	< 1 %	4 %	very common

[a] Frequency category is reported only for the oseltamivir group.

Treatment and prevention of influenza in children ≥ 1 year of age:

A total of 1481 children (including otherwise healthy children aged 1–12 and asthmatic children aged 6–12) participated in clinical studies of oseltamivir given for the treatment of influenza. A total of 859 children received treatment with oseltamivir suspension. The ADR that occurred in ≥ 1% of children aged 1 to 12 years receiving oseltamivir in the clinical trials for treatment of naturally acquired influenza (n = 859), and whose incidence is at least 1% higher on Oseltamivir Capsules compared to placebo (n = 622), is vomiting (16% on oseltamivir vs. 8% on placebo). Amongst the 148 children who received the recommended dose of Oseltamivir Capsules once daily in a post-exposure prophylaxis study in households (n = 99), and in a separate 6–week paediatric prophylaxis study (n = 49), vomiting was the most frequent ADR (8% on oseltamivir vs. 2% in the no prophylaxis group). Oseltamivir Capsules was well tolerated in these studies and the adverse events noted were consistent with those previously observed in paediatric treatment studies.

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

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

Eye disorders
Frequency not known: visual disturbance.

Cardiac disorders
Frequency not known: cardiac arrhythmia.

Gastrointestinal disorders
Frequency not known: gastrointestinal bleedings and hemorrhagic colitis.

Hepatobiliary disorders
Frequency not known: Hepatobiliary 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.

Psychiatric disorder/Nervous system disorder
Frequency not known: Hallucinations and convulsions

Additional information on special populations:
Treatment and Prophylaxis of Influenza in Geriatric patients There were no clinically relevant differences in the safety profile of the 942 subjects, 65 years of age and older, who received Oseltamivir Capsules or placebo, compared with the younger 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.

Overdose

Reports of overdoses with Oseltamivir Capsules have been received from clinical trials and during post-marketing experience. In the majority of cases reporting overdose, no adverse events were reported.Adverse events reported following overdose were similar in nature and distribution to those observed with therapeutic doses of Oseltamivir Capsules, described in Undesirable Effects

PHARMACOLOGICAL PROPERTIES

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 primarily important for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body. It has also been suggested that neuraminidase can play a role in viral entry into uninfected cells.

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

Treatment of Influenza
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. Patients who were found to carry oseltamivir-resistant virus generally did so transiently and showed no worsening of the underlying symptoms. In some pediatric patients, oseltamivir-resistant virus was detected for a prolonged period compared to patients carrying oseltamivir-sensitive virus; however these patients showed no prolongation of influenza symptoms.

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.

Prophylaxis of Influenza

There has been no evidence for emergence of drug resistance associated with the use of Oseltamivir Capsules 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 rate of emergence of resistance may be higher in the youngest age groups, and in immunosupressed 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).

Clinical and surveillance data:
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. Oseltamivir-resistant viruses isolated from oseltamivir-treated patients and oseltamivir resistant laboratory strains of influenza viruses have been found to contain mutations in N1and 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.

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 ºC, accompanied by at least one respiratorysymptom (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 ≤ 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 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 ≤ 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.

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 Posology and method of administration.

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 Posology and method of administration).

Children ≥1 year of age
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.

Geriatric Population
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. Halflives 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 Posology and method of administration).

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

Nonclinical 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 in its adopted therapeutic indications.

Reproductive Toxicity

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 milk. Limited data indicate that oseltamivir and the active metabolite are excreted in human milk. Extrapolation of the animal data provides estimates of 0.01 mg/day and 0.3 mg/day for the respective compounds. A potential for skin sensitisation to oseltamivir was observed in a "maximisation" test in guinea pigs. Approximately 50 % of the animals treated with the unformulated active 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).

PHARMACEUTICAL PARTICULARS

List of excipients
Pregelatinised maize starch, Povidone K-30, Croscarmellose sodium, Purified talc, Sodium stearyl fumarate. The composition of capsules are Gelatin, Iron oxide red (30 mg & 75 mg capsules), Iron oxide yellow (30 mg and 75 mg capsules), Iron oxide black (45 mg and 75 mg capsules), Titanium dioxide and Black ink (Tekprint SW-9008)

Incompatibilities
Not applicable.

Special precautions for storage
Do not store above 30°C
Protect from Moisture
This medicine should not be used after the expiry date (EXP) shown on the pack.

Nature and contents of container
Capsules: One box contains 10 capsules in a triplex blister pack (PVC/PE/PVDC, sealed with aluminium foil).

Special instructions for use, handling and disposal
Capsules: No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

Manufactured by:
MSN Laboratories Private Limited,
Formulation Division, Unit-II,
Sy.no. 1277, 1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy (District),
Telangana - 509 228, India.

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