OLTAVIR*–75

℞ Oseltamivir Capsules IP 75 mg

COMPOSITION

Each hard gelatin capsule contains:

Oseltamivir Phosphate IP ..... 98.5 mg
equivalent to Oseltamivir ..... 75 mg

Approved colours used in empty capsule shell.
Excipients ..... q.s.

PHARMACEUTICAL FORM

Oral capsule

CLINICAL PARTICULARS

Therapeutic Indications

OLTAVIR is indicated for treatment of Influenzae, for Prophylaxis of Influenzae in adult and children >14 years of age.

Posology and Method of Administration

The capsules may be taken with or without food; however, tolerability may be enhanced if Oltavir is taken with food.

Recommended Dosage for Adults, and adolescents 14 years and over

Treatment: The recommended oral dose is 75 mg oseltamivir twice daily for 5 days for adolescents (14 years and over) and adults.

Body Weight	*Recommended dose for 5 days*
> 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 dose for prevention of influenza following close contact with an infected individual is 75 mg oseltamivir once daily for 10 days for adolescents (14 years and over) and adults.

Body Weight	**Recommended dose for 5 days**
> 40 kg	75 mg once daily

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.

Recommended Dosage for People with 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.

Recommended Dosage for People with Renal impairment

Treatment of influenza: Dose adjustment is recommended for adults and adolescents (14 years and over) 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 (no data available)
Haemodialysis patients	30 mg after each haemodialysis 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 (14 years and over) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	**Recommended dose for treatment**
> 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 (no data available)
Haemodialysis patients	30 mg after every second haemodialysis 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.

There is insufficient clinical data available in infants and children (12 years of age and younger) with renal impairment to be able to make any dosing recommendation.

Elderly

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

Immunocompromised patients

Treatment: The recommended oral dose is 75 mg oseltamivir twice daily for 10 days for adults. Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Seasonal prophylaxis: Longer duration of seasonal prophylaxis up to 12 weeks has been evaluated in immunocompromised patients.

Contraindications

OLTAVIR is contraindicated in patients with a known serious hypersensitivity to oseltamivir or any of the components of the product. Severe allergic reactions have included anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme.

Special Warnings and Precautions for Use

The appropriate use of **OLTAVIR** 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 aged 1 year or older.

OLTAVIR is not a substitute for influenza vaccination. The use of antivirals for the treatment and prevention of influenza should be determined on the basis of official recommendations. Decisions regarding the use of oseltamivir for treatment and prophylaxis should take into consideration what is known about the characteristics of the circulating influenza viruses, available information on influenza drug susceptibility patterns for each season and the impact of the disease in different geographical areas and patient populations 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.

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 has been shown to be highly variable. Therefore, prescribers should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use Oseltamivir.

Severe concomitant condition

No information is available regarding the safety and efficacy of oseltamivir in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalisation.

Immunocompromised patients

The efficacy of oseltamivir in either treatment or prophylaxis of influenza in immunocompromised patients has not been firmly established. However, the duration of treatment of influenza in immunocompromised adult patients should be 10 days, as there are no studies of a shorter course of oseltamivir in this patient group. Cardiac / respiratory disease

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

Severe renal impairment

Dose adjustment is recommended for both treatment and prevention in adolescents (>14 years of age) and adults with severe renal impairment. There is insufficient clinical data available in infants.

Neuropsychiatric events

Neuropsychiatric events have been reported during administration of Oseltamivir in patients with influenza, especially in children and adolescents. These events are also experienced by patients with influenza without oseltamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient.

Drug Interactions

Influenza Vaccines

The concurrent use of oseltamivir with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of the potential for interference between these products, LAIV should not be administered within 2 weeks before or 48 hours after administration of oseltamivir, unless medically indicated.

Inactivated influenza vaccine can be administered at any time relative to the use of oseltamivir.

Overall Drug Interaction Profile

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems, suggest that clinically significant drug interactions via these mechanisms are unlikely.

Probenecid

No dose adjustment is required when co-administering with probenecid in patients with normal renal function. Co-administration of probenecid, a potent inhibitor of the anionic pathway of renal tubular secretion, results in an approximate 2-fold increase in exposure to the active metabolite of oseltamivir.

Amoxicillin

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

Renal Elimination

Clinically important drug interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these substances, the elimination characteristics of the active metabolite (glomerular filtration and anionic tubular secretion) and the excretion capacity of these pathways. However, care should be taken when prescribing oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Additional Information

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

Use in Special Population

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with Oseltamivir in pregnant women to inform a drug-associated risk of adverse developmental outcomes. Available published epidemiological

data suggest that Oseltamivir, taken in any trimester, is not associated with an increased risk of birth defects. However, these studies individually are limited by small sample sizes, use of different comparison groups, and some lacked information on dose, which preclude a definitive assessment of the risk. In animal reproduction studies with Oseltamivir, no adverse developmental effects were observed at clinically relevant exposures.

The background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Pregnant women are at higher risk of severe complications from influenza, which may lead to adverse pregnancy and/or fetal outcomes including maternal death, still births, birth defects, preterm delivery, low birth weight and small for gestational age.

Data

Human Data

Published prospective and retrospective observational studies of more than 5,000 women exposed to Oseltamivir during pregnancy, including more than 1,000 women exposed in the first trimester, suggest that the observed rate of congenital malformations was not increased above the rate in the general comparison population, regardless of when therapy was administered during the gestational period. However, individually, none of these studies had adequate sample sizes and some lacked information on dose, which preclude a definitive assessment of the risk.

Animal Data

Oseltamivir was administered orally during organogenesis to pregnant rats (at 50, 250, or 1500 mg/kg/day on gestation days 6 to 17) and rabbits (at 50, 150, or 500 mg/kg/day on gestation days 6 to 18). In rats, embryo-fetal effects consisting of an increased incidence of minor skeletal malformations were observed at a maternally toxic dose (1500 mg/kg/day), resulting in systemic drug exposures (based on AUC for oseltamivir carboxylate) 190 times human exposures at the maximum recommended human dose (MRHD) of Oseltamivir (75 mg twice a day). In the rabbit study, embryo-fetal effects consisting of an increased incidence of minor skeletal abnormalities and variants were observed at maternally toxic doses (≥150 mg/kg/day) resulting in systemic exposures (based on AUC for oseltamivir carboxylate) ≥8 times human exposures at the MRHD of Oseltamivir.

In prenatal and postnatal development studies in rats, oseltamivir was administered orally (at 50, 250, 500, or 1500 mg/kg/day) from organogenesis through late gestation, delivery, and lactation (gestation day 6 to postpartum/lactation day 20). Prolonged parturition duration and reduced offspring viability were observed at a maternally toxic dose (1500 mg/kg/day). No adverse maternal or offspring effects were observed at doses ≤500 mg/kg/day, resulting in systemic drug exposures (based on AUC for oseltamivir carboxylate) 44 times human exposures at the MRHD of Oseltamivir.

Lactation

Risk Summary

Based on limited published data, oseltamivir and oseltamivir carboxylate have been shown to be present in human milk at low levels considered unlikely to lead to toxicity in the breastfed infant. Postmarketing experience has not reported any information to suggest serious adverse effects of oseltamivir exposure via breast milk in infants. It is not known if oseltamivir affects human milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Oseltamivir and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Pediatric Use

Treatment of Influenza

Kindly refer to Posology and method of administration:

• >14 years of age: Safety and efficacy in adolescent patients >14 years of age was supported by adequate and well-controlled trials in adults and adolescents and younger pediatric patients and safety data in adolescents treated with Oseltamivir in a study of treatment and prophylaxis.

Geriatric Use

Treatment of Influenza of the 4,765 adults in clinical trials of Oseltamivir for the treatment of influenza, 948 (20%) were 65 years and older, while 329 (7%) were 75 years and older. In three double-blind, placebo-controlled trials in the treatment of influenza in patients at least 65 years old, that enrolled 741 subjects (374 received placebo and 362 received Oseltamivir), no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported 12 clinical experience has not identified differences in responses between the elderly and younger subjects.

Prophylaxis of Influenza

Of the 4,603 adults in clinical trials of Oseltamivir for the prophylaxis of influenza, 1,046 (23%) were 65 years and older, while 719 (16%) were 75 years and older. In a randomized, placebo-controlled trial in elderly residents of nursing homes who took Oseltamivir for up to 42 days for the prophylaxis of influenza (Oseltamivir n=276, placebo n=272), no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

Renal Impairment

Patients with renal impairment had higher blood levels of oseltamivir carboxylate compared to patients with normal renal function which may increase the risk of Oseltamivir-associated adverse reactions. Therefore, dosage adjustment is recommended for patients with a serum creatinine clearance between 10 and 60 mL/ minute and for patients with endstage renal disease (ESRD) undergoing routine hemodialysis or continuous peritoneal dialysis treatment. Oseltamivir is not recommended for patients with ESRD not undergoing dialysis.

Treatment of influenza: Dose adjustment is recommended for adults and adolescents (14 years and over) 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 (no data available)
Haemodialysis patients	30 mg after each haemodialysis 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 (14 years and over) with moderate or severe renal impairment as detailed in the table below.

Creatinine clearance	Recommended dose for treatment
> 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 (no data available)
Haemodialysis patients	30 mg after every second haemodialysis 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.

There is insufficient clinical data available in infants and children (12 years of age and younger) with renal impairment to be able to make any dosing recommendation.

Hepatic Impairment

No dosage adjustment is required in patients with mild to moderate hepatic impairment. The safety and pharmacokinetics in patients with severe hepatic impairment have not been evaluated.

Use in Patients with Chronic Conditions

Efficacy of Oseltamivir in the treatment of influenza in patients with chronic cardiac disease and/or respiratory disease was evaluated in one randomized, placebo-controlled clinical trial. Efficacy in this population, as measured by time to alleviation of all symptoms, was not established, but no new safety signals were identified.

No clinical trial data are available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalization.

Immunocompromised Patients

Efficacy of Oseltamivir for the treatment or prophylaxis of influenza has not been established in immunocompromised patients. Safety of Oseltamivir has been demonstrated for up to 12 weeks for prophylaxis of influenza in immunocompromised patients.

Treatment: The recommended oral dose is 75 mg oseltamivir twice daily for 10 days for adults. Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.

Seasonal prophylaxis: Longer duration of seasonal prophylaxis up to 12 weeks has been evaluated in immunocompromised patients.

Effects on ability to drive and use machines

OLTAVIR has no influence on the ability to drive and use machines.

Undesirable effects

Summary of the Safety Profile

The overall safety profile of oseltamivir is based on data from 6,049 adult/adolescent and 1,473 paediatric patients treated with oseltamivir or placebo for influenza, and on data from 3,990 adult/adolescent and 253 paediatric patients receiving oseltamivir or placebo/no treatment for the prophylaxis of influenza in clinical trials. In addition, 475 immunocompromised patients (including 18 children — 10 on oseltamivir and 8 on placebo) received oseltamivir or placebo for the prophylaxis of influenza.

In adults/adolescents, the most commonly reported adverse reactions were nausea and vomiting in the treatment studies, and nausea in the prevention studies. The majority of these adverse reactions were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1 to 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 rarely reported since oseltamivir has been marketed: anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding, and neuropsychiatric disorders.

The adverse reactions listed in the tables below fall into the following categories: 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), and very rare (<1/10,000). 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

In adult/adolescent treatment and prevention studies, adverse reactions that occurred the most frequently 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) are shown below.

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 seen in the treatment studies, despite a longer duration of dosing in the prophylaxis studies.

Adverse Reactions in Studies Investigating Oseltamivir for the Treatment and Prevention of Influenza in Adults and Adolescents or through Postmarketing Surveillance

System Organ Class	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 bleeding Haemorrhagic colitis
Hepatobiliary disorders			Elevated liver enzymes	Fulminant hepatitis Hepatic failure Hepatitis
Skin and subcutaneous tissue disorders			Eczema Dermatitis Rash Urticaria	Angioneurotic oedema, Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis
General disorders and administration site conditions		Pain Dizziness (including vertigo) Fatigue Pyrexia Pain in limb		

Description of Selected Adverse Reactions

Psychiatric Disorders and Nervous System Disorders

Influenza can be associated with a variety of neurologic and behavioural symptoms, which can include events such as hallucinations, delirium and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

In patients with influenza who were receiving 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 in patients with influenza-like illness, have been reported. These cases include fatal fulminant hepatitis/hepatic failure.

Elderly Patients and Patients with Chronic Cardiac and/or Respiratory Disease

The population included in the influenza treatment studies is comprised of otherwise healthy adults/adolescents and patients 'at risk' (patients at higher risk of developing complications associated with influenza, e.g. 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 otherwise healthy adults/adolescents. Those events reported numerically more frequently in subjects taking oseltamivir compared with placebo were nausea, vomiting, bronchitis, insomnia, and vertigo.

Immunocompromised Patients

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

Children with Pre-existing Bronchial Asthma

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

Additional

Other adverse reactions identified during post-approval use of oseltamivir include swelling of the face or tongue, allergy, hypothermia, seizure, and aggravation of diabetes. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to oseltamivir exposure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com

Overdose

Reports of overdoses with oseltamivir have been received from clinical trials and during postmarketing experience. In the majority of cases reporting overdose, no adverse events were reported. Adverse events reported following overdose were similar in nature to those observed with therapeutic doses of oseltamivir.

No specific antidote is known.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Oseltamivir is an antiviral drug with activity against influenza virus. It is an ethyl ester pro-drug, requiring ester hydrolysis for conversion to the active form, 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.

Pharmacodynamic Properties

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication in vitro. Oseltamivir given orally inhibits influenza A and B virus replication and pathogenicity in vivo in animal models of influenza infection at antiviral exposures similar to that achieved in man with 75 mg twice daily.

Antiviral activity of oseltamivir was supported for influenza A and B by experimental challenge studies in healthy volunteers.

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0.1 nM to 1.3 nM, and for influenza B was 2.6 nM. Higher IC50 values for influenza B, up to a median of 8.5 nM, have been observed in published studies.

Clinical studies

Treatment of influenza infection

The indication is based on clinical studies of naturally occurring influenza in which the predominant infection was influenza A.

Oseltamivir is effective only against illnesses caused by influenza virus. Statistical analyses are therefore presented only for influenza-infected subjects. In the pooled treatment study population, which included both influenza-positive and -negative subjects (ITT), primary efficacy was reduced proportionally to the number of influenza-negative individuals. In the overall treatment population, influenza infection was confirmed in 67% (range 46% to 74%) of the recruited patients. Of the older subjects, 64% were influenza-positive and of those with chronic cardiac and/or respiratory disease 62% were influenza-positive. In all phase III treatment studies, patients were recruited only during the period in which influenza was circulating in the local community.

Adults and adolescents 14 years of age and older: Patients were eligible if they reported within 36 hours of onset of symptoms, had fever $\geq$ 37.8°C, accompanied by at least one respiratory symptom (cough, nasal symptoms or sore throat) and at least one systemic symptom (myalgia, chills/sweats, malaise, fatigue or headache). In a pooled analysis of all influenza-positive adults and adolescents (N = 2,413) enrolled into treatment studies, oseltamivir 75 mg twice daily for 5 days reduced the median duration of influenza illness by approximately one day from 5.2 days (95% CI 4.9 – 5.5 days) in the placebo group to 4.2 days (95% CI 4.0 – 4.4 days; $p \leq 0.0001$).

The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7% (135/1,063) in the placebo group to 8.6 % (116/1,350) in the oseltamivir treated population (p = 0.0012).

Treatment of influenza in high risk populations: The median duration of influenza illness in older subjects ($\geq$ 65 years) and in subjects with chronic cardiac and/or respiratory disease receiving oseltamivir 75 mg twice daily for 5 days was not reduced significantly. The total duration of fever was reduced by one day in the groups treated with oseltamivir. In influenza-positive older people, oseltamivir significantly reduced the incidence of specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics from 19% (52/268) in the placebo group to 12% (29/250) in the oseltamivir treated population (p = 0.0156).

In influenza-positive patients with chronic cardiac and/or respiratory disease, the combined incidence of lower respiratory tract complications (mainly bronchitis) treated with antibiotics was 17% (22/133) in the placebo group and 14% (16/118) in the oseltamivir treated population (p = 0.5976).

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

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

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

The median time to resolution of symptoms (TTRS) was similar between the standard dose group (103 hours [90% CI 75.4-110.0]) and double dose group (104 hours [90% CI 65.8-131.0]). The proportion of patients with secondary infections in the standard dose group and double dose group was comparable (8.2% vs 5.1%).

Prevention of influenza

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households and two seasonal prevention studies. The primary efficacy parameter for all of these studies was the incidence of laboratory-confirmed influenza. The virulence of influenza epidemics is not predictable and varies within a region and from season to season, therefore the number needed to treat (NNT) in order to prevent one case of influenza illness varies.

Post-exposure prevention: In a study in contacts (12.6% vaccinated against influenza) of an index case of influenza, oseltamivir 75 mg once daily was started within 2 days of onset of symptoms in the index case and continued for seven days. Influenza was confirmed in 163 out of 377 index cases. Oseltamivir significantly reduced the incidence of clinical influenza illness occurring in the contacts of confirmed influenza cases from 24/200 (12%) in the placebo group to 2/205 (1%) in the oseltamivir group (92% reduction [95% CI 6 – 16; $p \leq 0.0001$]). The number needed to treat (NNT) in contacts of true influenza cases was 10 (95% CI 9 – 12) and was 16 (95% CI 15 – 19) in the whole population (ITT) regardless of infection status in the index case.

The efficacy of oseltamivir in preventing naturally occurring influenza illness has been demonstrated in a post-exposure prevention study in households that included adults, adolescents, and children

aged 1 to 12 years, both as index cases and as family contacts. The primary efficacy parameter for this study was the incidence of laboratory-confirmed clinical influenza in the households. Oseltamivir prophylaxis lasted for 10 days. In the total population, there was a reduction in the incidence of laboratory-confirmed clinical influenza in households from 20% (27/136) in the group not receiving prevention to 7% (10/135) in the group receiving prevention (62.7% reduction [95% CI 26.0 – 81.2; p = 0.0042]). In households of influenza- infected index cases, there was a reduction in the incidence of influenza from 26% (23/89) in the group not receiving prevention to 11% (9/84) in the group receiving prevention (58.5% reduction [95% CI 15.6 – 79.6; p = 0.0114]).

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

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

Prevention during an influenza epidemic in the community: In a pooled analysis of two other studies conducted in unvaccinated otherwise healthy adults, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 25/519 (4.8%) in the placebo group to 6/520 (1.2%) in the oseltamivir group (76% reduction [95% CI 1.6 – 5.7; p = 0.0006]) during a community outbreak of influenza. The NNT in this study was 28 (95% CI 24 – 50).

A study in older people in nursing homes, where 80% of participants received vaccine in the season of the study, oseltamivir 75 mg once daily given for 6 weeks significantly reduced the incidence of clinical influenza illness from 12/272 (4.4%) in the placebo group to 1/276 (0.4%) in the oseltamivir group (92% reduction [95% CI 1.5 – 6.6; p = 0.0015]). The NNT in this study was 25 (95% CI 23 – 62).

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

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

The antiviral activity and neuraminidase inhibitory activity of oseltamivir carboxylate against laboratory strains and clinical isolates of influenza virus was determined in cell culture The concentrations of oseltamivir carboxylate required for inhibition of the influenza virus were highly variable, depending on the assay method used and the virus tested. The 50% and 90% effective concentrations (EC_{50} and EC_{90}) were in the range of 0.0008 microM to >35 microM and 0.004 microM to >100 microM, respectively (1 microM = 0.284 mcg/mL).

The relationship between the antiviral activity in cell culture and the inhibition of the influenza virus replication in humans has not been established.

Resistance

Influenza A virus isolates with reduced susceptibility to oseltamivir carboxylate have been recovered by serial passage of virus in cell culture in the presence of increasing concentrations of oseltamivir carboxylate. Reduced susceptibility of influenza virus to inhibition by oseltamivir carboxylate may be conferred by amino acid substitutions in the viral neuraminidase and/or hemagglutinin proteins.

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

Patient Population	Patients with Resistance Mutations (%)	
	Phenotyping*	Geno- and Phenotyping*
Adults and adolescents	0.62% (14/2253)	0.67% (15/2253)
Children (1-12 years)	3.89% (66/1698)	4.24% (72/1698)
Infants (<1year)	18.31% (13/71)	18.31% (13/71)

** 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 conducted to date in post-exposure (7 days), post-exposure within household groups (10 days) and seasonal (42 days) prevention of influenza in immunocompetent patients. There was no resistance observed during a 12-week prophylaxis study in immunocompromised patients.

Hemagglutinin (HA) substitutions selected in cell culture and associated with reduced susceptibility to oseltamivir include (influenza virus subtype-specific numbering) A11T, K173G, and R453M in H3N2; and H99Q in influenza B virus (Yamagata lineage). In some cases, HA substitutions were selected in conjunction with known NA resistance substitutions and may contribute to reduced susceptibility to oseltamivir; however, the impact of HA substitutions on antiviral activity of oseltamivir in humans is unknown and likely to be strain dependent.

The frequency of resistance selection to oseltamivir and the prevalence of such resistant virus vary seasonally and geographically.

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.

Circulating seasonal influenza strains expressing neuraminidase resistance-associated substitutions have been observed in individuals who have not received oseltamivir treatment. Since 2007 naturally occurring resistance associated with the H275Y mutation in seasonal H1N1 strains has been sporadically detected. The susceptibility to oseltamivir and the prevalence of such viruses appear to vary seasonally and geographically. The oseltamivir resistance-associated substitution H275Y was found in >99% of US/ Europe circulating 2008 H1N1 influenza isolates. 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. Prescribers should consider available information from the Centers for Disease Control and Prevention (CDC) on influenza drug susceptibility patterns and treatment effects when deciding whether to use oseltamivir.

Cross-resistance

Cross-resistance between oseltamivir and zanamivir has been observed in neuraminidase biochemical assays. The H275Y (N1 numbering) or N294S (N2 numbering) oseltamivir resistance-associated substitutions observed in the N1 neuraminidase subtype, and the E119V or N294S oseltamivir resistance-associated substitutions observed in the N2 subtype (N2 numbering), are associated with reduced susceptibility to oseltamivir but not zanamivir. The Q136K and K150T zanamivir resistance-associated substitutions observed in N1 neuraminidase, or the S250G zanamivir resistance-associated substitutions observed in influenza B, confer reduced susceptibility to zanamivir but not oseltamivir. The R292K oseltamivir resistance-associated substitution observed in N2, and the I222T, D198E/N, R371K, or G402S oseltamivir resistance-associated substitutions observed in influenza B neuraminidase, confer reduced susceptibility to both oseltamivir and zanamivir. In general, amino acid substitutions at neuraminidase catalytic residues confer cross-resistance to other neuraminidase inhibitors while substitutions at framework residues may or may not confer cross-resistance. No single amino acid substitution has been identified that could confer cross-resistance between the neuraminidase inhibitor class (oseltamivir, zanamivir) and the M2 ion channel inhibitor class (amantadine, rimantadine). However, a virus may carry a neuraminidase inhibitor associated substitution in neuraminidase and an M2 ion channel inhibitor associated substitution in M2 and may, therefore, be resistant to both classes of inhibitors. The clinical relevance of phenotypic cross-resistance evaluations has not been established.

Immune Response

No influenza vaccine interaction study has been conducted. In studies of naturally acquired and experimental influenza, treatment with oseltamivir did not impair normal humoural antibody response to infection.

Pharmacokinetics

Adults

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted, predominantly by hepatic esterases, to oseltamivir carboxylate (active metabolite). At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate. Exposure to oseltamivir is less than 5% of the total exposure after oral dosing as described in table below.

Mean (% CV) Pharmacokinetic Parameters of Oseltamivir and Oseltamivir Carboxylate Following Multiple Dosing of 75 mg Capsules Twice Daily (n=20)		
Parameter	**Oseltamivir**	**Oseltamivir Carboxylate**
C_{max} (ng/mL)	65 (26)	348 (18)
AUC_{0-12h} (ng•h/mL)	112 (25)	2,719 (20)

Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily (about 6.7 times the maximum recommended oseltamivir dosage).

Co-administration with food has no significant effect on the peak plasma concentration (551 ng/mL under fasted conditions and 441 ng/mL under fed conditions) and the area under the plasma concentration time curve (6,218 ng•h/mL under fasted conditions and 6,069 ng•h/mL under fed conditions) of oseltamivir carboxylate.

The volume of distribution (V_{ss}) of oseltamivir carboxylate, following intravenous administration in 24 subjects, ranged between 23 to 26 litres, 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 low (3%). The binding of oseltamivir to human plasma protein is 42%, which is insufficient to cause significant displacement-based drug interactions.

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. Neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome (CY)) P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Absorbed oseltamivir is primarily (>90%) eliminated by conversion to oseltamivir carboxylate. Plasma concentrations of oseltamivir declined with a half-life of 1 to 3 hours in most subjects after oral administration. Oseltamivir carboxylate is not further metabolized and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate declined with a half-life of 6 to 10 hours in most subjects after oral administration.

Oseltamivir carboxylate is eliminated entirely (>99%) by renal excretion. Renal clearance (18.8 L/h) exceeds the glomerular filtration rate (7.5 L/h), indicating that tubular secretion (via organic anion transporter) occurs, in addition to glomerular filtration. Less than 20% of an oral radiolabelled dose is eliminated in the faeces.

Renal Impairment

Administration of 100 mg of oseltamivir twice daily (about 1.3 times the maximum recommended dosage) for 5 days to subjects with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function.

Population-derived pharmacokinetic parameters were determined for patients with varying degrees of renal function including ESRD patients on hemodialysis. Median simulated exposures of oseltamivir carboxylate for recommended treatment and prophylaxis regimens are provided in table below. The pharmacokinetics of oseltamivir have not been studied in ESRD patients not undergoing dialysis.

Simulated Median Treatment Exposure Metrics of Oseltamivir Carboxylate in Patients with Normal Renal Function, with Renal Impairment and ESRD Patients on Hemodialysis

Renal Function/ Impairment	Normal Creatinine Clearance 90-140 mL/ min (n=57)	Mild Creatinine Clearance 60-90 mL/ min (n=45)	Moderate Creatinine Clearance 30-60 mL/ min (n=13)	Severe Creatinine Clearance 10-30 mL/ min (n=11)	ESRD Creatinine Clearance <10 mL/min on Hemodialysis (n=14)
Recommended Treatment Regimens					
PK exposure parameter	**75 mg twice daily**	**75 mg twice daily**	**30 mg twice daily**	**30 mg once daily**	**30 mg every HD cycle**
C_{max} (ng/mL)	145	253	180	219	221
C_{max} (ng/mL)	298	464	305	477	1170
AUC_{48} (ng h/mL)*	11224	15476	12008	16818	23200
Recommended Prophylaxis Regimens					
PK exposure parameter	**75 mg twice daily**	**75 mg twice daily**	**30 mg twice daily**	**30 mg once daily**	**30 mg every HD cycle**
C_{max} (ng/mL)	39	62	37	70	42
C_{max} (ng/mL)	213	311	209	377	903
AUC_{48} (ng h/mL)*	5294	8336	6262	9317	11200

*AUC normalized to 48 hours

In continuous ambulatory peritoneal dialysis (CAPD) patients, the peak concentration of oseltamivir carboxylate following a single 30 mg dose of oseltamivir or once weekly oseltamivir was approximately 3 fold higher than in patients with normal renal function who received 75 mg twice daily. The plasma concentration of oseltamivir carboxylate on Day 5 (147 ng/mL) following a single 30 mg dose in CAPD patients is similar to the predicted C_{min} (160 ng/mL) in patients with normal renal function following 75 mg twice daily. Administration of 30 mg once weekly to CAPD patients resulted in plasma concentrations of oseltamivir carboxylate at the 168 hour blood sample of 63 ng/mL, which were comparable to the C_{min} in patients with normal renal function receiving the approved regimen of 75 mg once daily (40 ng/mL).

Hepatic Impairment

In clinical studies, oseltamivir carboxylate exposure was not altered in patients with mild or moderate hepatic impairment.

Geriatric

Exposure to oseltamivir carboxylate at the steady state was 25 to 35% higher in geriatric patients (age range: 65 to 78 years) compared with young adults given comparable doses of oseltamivir. Half-lives observed in the geriatric patients were similar to those seen in young adults. Based on drug exposure and tolerability, dose adjustments are not required for geriatric patients for either treatment or prophylaxis unless there is evidence of moderate or severe renal impairment (creatinine clearance <60 ml/min).

Pregnant Women

A pooled population pharmacokinetic analysis indicates that the oseltamivir dosage regimen results in lower exposure (30% on average across all trimesters) to the active metabolite in pregnant women (n=59) compared to non-pregnant women (n=33). 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 PROPERTIES

Carcinogenesis, Mutagenesis, Impairment of Fertility

In 2-year carcinogenicity studies in mice and rats given daily oral doses of the prodrug oseltamivir phosphate up to 400 mg/kg and 500 mg/kg, respectively, the prodrug and the active form oseltamivir carboxylate induced no statistically significant increases in tumors over controls. The mean maximum daily exposures to the prodrug in mice and rats were approximately 130- and 320-fold, respectively, greater than those in humans at the recommended clinical dose based on AUC comparisons. The respective safety margins of the exposures to the active oseltamivir carboxylate were 15- and 50-fold. Oseltamivir was found to be non-mutagenic in the Ames test and the human lymphocyte chromosome assay with and without enzymatic activation and negative in the mouse micronucleus test. It was found to be positive in a Syrian Hamster Embryo (SHE) cell transformation test. Oseltamivir carboxylate was non-mutagenic in the Ames test and the L5178Y mouse lymphoma assay with and without enzymatic activation and negative in the SHE cell transformation test. In a fertility and early embryonic development study in rats, doses of oseltamivir at 50, 250, and 1500 mg/kg/day were administered to females for 2 weeks before mating, during mating and until day 6 of pregnancy. Males were dosed for 4 weeks before mating, during mating, and for 2 weeks after mating. There were no effects on fertility, mating performance or early embryonic development at any dose level. The highest dose in this study was approximately 115 times the human systemic exposure (AUC0-24h) of oseltamivir carboxylate that occurs after administration of the maximum recommended human dose.

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 in its adopted therapeutic indications.

Teratology studies have been conducted in rats and rabbits at doses of up to 1,500 mg/kg/day and 500 mg/kg/day, respectively. No effects on foetal development were observed. A rat fertility study up to a dose of 1,500 mg/kg/day demonstrated no adverse reactions on either sex. In pre- and post-natal rat studies, prolonged parturition was noted at 1,500 mg/kg/day: the safety margin between human exposure and the highest no-effect dose (500 mg/kg/day) in rats is 480-fold for oseltamivir and 44-fold for the active metabolite, respectively. Foetal exposure in the rats and rabbits was approximately 15 to 20% of that of the mother.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk. Limited data indicate that oseltamivir and the active metabolite are excreted in human milk. Extrapolation of the animal data provides estimates of 0.01 mg/day and 0.3 mg/day for the respective compounds.

Animal Toxicology or Pharmacology

A potential for skin sensitisation to oseltamivir was observed in a “maximisation” test in guinea pigs. Approximately 50% of the animals treated with the unformulated active substance showed erythema after challenging the induced animals. Reversible irritancy of rabbits eyes was detected.

Whereas very high oral single doses of oseltamivir phosphate salt, up to the highest dose tested (1,310 mg/ kg), had no adverse reactions in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death. These reactions were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse reactions were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days post partum).

DESCRIPTION

Oseltamivir phosphate is a white crystalline solid with the chemical name (3R,4R,5S)-4-acetylamino-5-amino- 3(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate (1:1). The chemical formula is $C_{16}H_{28}N_2O_4$ (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable

Packaging Information

OLTAVIR Capsules is available in a blister pack of 10 capsules.

Storage and Handling Instructions

Store protected from moisture, at a temperature not exceeding 30°C.

Keep the medicine out of reach of children.

Marketed by :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, ‘B’ Wing, Hind Cycle Road,
Worli, Mumbai - 400 030. India.

*Trade Mark under Registration

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Note: This prescribing information is applicable for India Market only.