To be sold by retail on the prescription of a Registered Medical Practitioner only.

OSELOW

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1. GENERIC NAME

Oseltamivir Phosphate Capsules IP 30 mg
Oseltamivir Phosphate Capsules IP 45 mg
Oseltamivir Phosphate Capsules IP 75 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oseltamivir phosphate hard capsules – 30 mg
Each Hard gelatin capsules contains Oseltamivir phosphate IP Equivalent to
Oseltamivir .... 30 mg

Oseltamivir phosphate hard capsules – 45 mg
Each Hard gelatin capsules contains Oseltamivir phosphate IP Equivalent to
Oseltamivir .... 45 mg

Oseltamivir phosphate hard capsules – 75 mg
Each Hard gelatin capsules contains Oseltamivir phosphate IP Equivalent to
Oseltamivir .... 75 mg

3. DOSAGE FORM AND STRENGTH

Oseltamivir phosphate is available as hard capsules 30 mg, 45 mg and 75 mg.

4. CLINICAL PARTICULARS

4.1. Indications

Treatment of influenza
Oseltamivir phosphate capsules are indicated for the treatment of acute, uncomplicated illness due to influenza A and B infection in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours.

Prophylaxis of Influenza
Oseltamivir phosphate capsules are indicated for the prophylaxis of influenza A and B in patients 1 year and older.

Limitations of Use

- Oseltamivir phosphate capsules are not a substitute for early influenza vaccination on an annual basis as recommended by the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices.
- Influenza viruses change over time. Emergence of resistance substitutions could decrease drug effectiveness. Other factors (for example, changes in viral virulence) might also diminish clinical benefit of antiviral drugs. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether to use oseltamivir phosphate capsules.
- Oseltamivir phosphate capsules are not recommended for patients with end-stage renal disease not undergoing dialysis.

4.2. Posology and Method of Administration

Posology
Oseltamivir phosphate hard capsules 75 mg doses can be administered as either
- one 75 mg capsule or
- one 30 mg capsule plus one 45 mg capsule.

Recommended Dosing
Initiate treatment with oseltamivir phosphate capsules within 48 hours of influenza symptom onset.

Adults and Adolescents (13 years of age and older)
The recommended oral dosage of oseltamivir phosphate capsules for treatment of influenza in adults and adolescents 13 years and older is 75 mg twice daily (one 75 mg capsule or 12.5 mL of oral suspension twice daily) for 5 days.

Pediatric Patients (2 weeks of age through 12 years of age)
Table 1 displays the recommended oral dosage of oseltamivir phosphate capsules for treatment of influenza in pediatric patients 2 weeks of age through 12 years of age and provides information about prescribing the capsule or the formulation for oral suspension.

Recommended Dosage for Prophylaxis of Influenza
Initiate post-exposure prophylaxis with oseltamivir phosphate capsules within 48 hours following close contact with an infected individual. Initiate seasonal prophylaxis with oseltamivir phosphate capsules during a community outbreak.

Adults and Adolescents (13 years of age and older)
The recommended dosage of oseltamivir phosphate capsules for prophylaxis of influenza in adults and adolescents 13 years and older is 75 mg orally once daily (one 75 mg capsule or 12.5 mL of oral suspension once daily) for at least 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak. In immunocompromised patients, oseltamivir phosphate capsules may be continued for up to 12 weeks. The duration of protection lasts for as long as oseltamivir phosphate capsules dosing is continued.

Pediatric Patients (1 year to 12 years of age)
Table 1 displays the recommended oral dosage of oseltamivir phosphate capsules for prophylaxis of influenza in pediatric patients 1 year to 12 years of age based on body weight and provides information about prescribing the capsule or the formulation for oral suspension. Prophylaxis in pediatric patients is recommended for 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak.

Table 1 Oseltamivir Phosphate Capsule Dosage Recommendations in Pediatric Patients for Treatment and Prophylaxis of Influenza

Weight	Treatment Dosage for 5 days	Prophylaxis Dosage for 10 days *	Number of Capsules to Dispense (Strength)‡
Patients from 2 weeks to less than 1 year of age			
Any weight	3 mg/kg twice daily	Not applicable	Not applicable
Patients 1 to 12 years of age based on body weight			
15 kg or less	30 mg twice daily	30 mg once daily	10 capsules (30 mg)
15.1 kg to 23 kg	45 mg twice daily	45 mg once daily	10 capsules (45 mg)
23.1 kg to 40 kg	60 mg twice daily	60 mg once daily	20 capsules (30 mg)
40.1 kg or more	75 mg twice daily	75 mg once daily	10 capsules (75 mg)

* Capsules or oral suspension can be used for 30 mg dosing.
‡ Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients.

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
Table 2 displays the dosage recommendations for the treatment and prophylaxis of influenza in adults with various stages of renal impairment (estimated creatinine clearance of less than or equal to 90 mL per minute). Dosage modifications are recommended in adults with an estimated creatinine clearance less than or equal to 60 mL per minute.

Table 2 Recommended Dosage Modifications for Treatment and Prophylaxis of Influenza in Adults with Renal Impairment or End Stage Renal Disease (ESRD) on Dialysis

Renal Impairment (Creatinine Clearance)	Recommended Treatment Regimen *	Recommended Prophylaxis Regimen *†
Mild (>60 to 90 mL/minute)	75 mg twice daily for 5 days	75 mg once daily
Moderate (>30 to 60 mL/minute)	30 mg twice daily for 5 days	30 mg once daily
Severe (>10 to 30 mL/minute)	30 mg once daily for 5 days	30 mg every other day
ESRD Patients on Hemodialysis (≤ 10 mL/minute)	30 mg immediately and then 30 mg after every hemodialysis cycle (treatment duration not to exceed 5 days)	30 mg immediately and then 30 mg after alternate hemodialysis cycles
ESRD Patients on Continuous Ambulatory Peritoneal Dialysis ‡ (≤10 mL/minute)	A single 30 mg dose administered immediately	30 mg immediately and then 30 mg once weekly
ESRD Patients not on Dialysis	Oseltamivir phosphate is not recommended	Oseltamivir phosphate is not recommended

* Capsules or oral suspension can be used for 30 mg dosing.
† The recommended duration for post-exposure prophylaxis is at least 10 days and the recommended duration for community outbreak (seasonal/pre-exposure) prophylaxis is up to 6 weeks (or up to 12 weeks in immunocompromised patients).
‡ Data derived from studies in continuous ambulatory peritoneal dialysis (CAPD) patients.

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.

Emergency Preparation of Oral Suspension from 75 mg Oseltamivir Phosphate Capsules
The following directions are provided for use only during emergency situations and when FDA approved, commercially manufactured oseltamivir phosphate for oral suspension is not available from wholesalers or the manufacturer.
The following emergency preparation instructions will provide one patient with enough oseltamivir phosphate for a 5-day course of treatment of influenza or a 10-day course of prophylaxis of influenza:
Step #1: Determine the dosage of oseltamivir phosphate for the patient then determine the total volume of oral suspension needed to be prepared (see Table 3).

Table 3 Emergency Preparation: Volume of Prepared Oral Sus pens ion (6 mg per mL) Based Upon Oseltamivir Phosphate Dose

Oseltamivir Phosphate Dose*	Total Volume to Prepare per Patient
15 mg or less	37.5 mL
30 mg	75 mL
45 mg	100 mL
60 mg	125 mL
75 mg	150 mL

* If the oseltamivir phosphate dose is between the doses listed, use the greater listed dose to determine the total volume of prepared oral suspension.

Step #2: Preparation must be performed with only one of the following vehicles (other vehicles have not been studied): Cherry Syrup (Humco), Ora-Sweet SF (sugar-free) (Paddock Laboratories), or simple syrup. Determine the number of capsules and the amount of water and vehicle needed to prepare the total volume (see Table 3) of prepared oral suspension (6 mg per mL) for a complete treatment or prophylaxis course (see Table 4).

Table 4 Emergency Preparation: Number of Oseltamivir Phosphate 75 mg Capsules and Amount of Water and Vehicle Needed to Prepare the Total Volume of a Prepared Oral Suspension (6 mg per mL)

Total Volume of Prepared Oral Sus pens ion	37.5 mL	75 mL	100 mL	125 mL	150 mL
Number of Oseltamivir Phosphate Capsules 75 mg (Total Strength)*	3 (225 mg)	6 (450 mg)	8 (600 mg)	10 (750 mg)	12 (900 mg)
Amount of Water	2.5 mL	5 mL	7 mL	8 mL	10 mL
Volume of Vehicle Cherry Syrup (Humco) OR Ora-Sweet SF (Paddock Laboratories) OR simple syrup	34.5 mL	69 mL	91 mL	115 mL	137 mL

* Includes overage to ensure all doses can be delivered

Step #3: Follow the instructions below for preparing the 75 mg oseltamivir phosphate capsules to produce the oral suspension (6 mg per mL):

- Place the specified amount of water into a polyethyleneterephthalate (PET) or glass bottle (see Table 4). Constitution in other bottle types is not recommended because there is no stability data with other bottle types.
- Carefully separate the capsule body and cap and pour the contents of the required number of oseltamivir phosphate 75 mg capsules into the PET or glass bottle.
- Gently swirl the suspension to ensure adequate wetting of the oseltamivir phosphate powder for at least 2 minutes.
- Slowly add the specified amount of vehicle to the bottle.
- Close the bottle using a child-resistant cap and shake well for 30 seconds to completely dissolve the active drug and to ensure homogeneous distribution of the dissolved drug in the resulting suspension. The active drug, oseltamivir phosphate, readily dissolves in the specified vehicles. The suspension is caused by inert ingredients of oseltamivir phosphate capsules which are insoluble in these vehicles.
- Put an ancillary label on the bottle indicating "Shake Well Before Use."
- Instruct the parent or caregiver that any unused suspension remaining in the bottle following completion of therapy must be discarded by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.
- Place a pharmacy label on the bottle that includes the patient's name, dosing instructions, drug name and any other required information to be in compliance with all State and Federal Pharmacy Regulations. Place an appropriate expiration date on the label according to storage conditions below.
- Include the recommended dosage on the pharmacy label as per Tables 1 and 2.
- Store the prepared oral suspension in glass or PET bottles either:
  - In a refrigerator [2° to 8°C (36° to 46°F)]: Stable for 5 weeks when stored in a refrigerator.
  - At room temperature [25°C (77°F)]: Stable for 5 days when stored at room temperature.

Method of administration
Oral Use
Patients who are unable to swallow capsules may receive appropriate doses of oseltamivir phosphate suspension.

4.3. Contraindications

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

4.4. Special Warnings and Precautions for Use

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

Neuropsychiatric events
Neuropsychiatric events have been reported during administration of Oseltamivir in patients with influenza, especially in children and adolescents. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease. These events are also experienced by patients with influenza without oseltamivir administration. Influenza can be associated with a variety of neurologic and behavioral symptoms that can include events such as hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient.

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.

Paediatric population
No data allowing a dose recommendation for premature children (< 36 weeks post-conceptual age) are currently available.

Severe renal impairment
Dose adjustment is recommended for both treatment and prevention in adolescents (13 to 17 years of age) and adults with severe renal impairment. There is insufficient clinical data available in infants and children (1 year of age or older) with renal impairment to be able to make any dosing recommendation.

4.5. Drug Interactions

Influenza Vaccines
Live Attenuated Influenza Vaccine
The concurrent use of oseltamivir phosphate with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of the potential for oseltamivir phosphate to inhibit replication of live vaccine virus and possibly reduce the efficacy of LAIV, avoid administration of LAIV within 2 weeks before or 48 hours after oseltamivir phosphate administration, unless medically indicated.
Inactivated Influenza Vaccine
Inactivated influenza vaccine can be administered at any time relative to use of oseltamivir phosphate.
Drugs without Clinically Significant Drug Interaction with Oseltamivir Phosphate
No dose adjustments are needed for either oseltamivir or the concomitant drug when coadministering oseltamivir with amoxicillin, acetaminophen, aspirin, cimetidine, antacids (magnesium and aluminum hydroxides and calcium carbonates), rimantadine, amantadine, or warfarin
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. Coadministration 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.

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).

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy
Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations, including congenital heart defects. The use of Oseltamivir may be considered during pregnancy if necessary and after considering the available safety and benefit information, and the pathogenicity of the circulating influenza virus strain.

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.

Breast-feeding:
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 sub-therapeutic dose to the infant. The developmental and health benefits of breastfeeding should be considered along with the pathogenicity of the circulating influenza virus strain, mother's clinical need for oseltamivir phosphate and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Fertility:
Based on preclinical data, there is no evidence that Oseltamivir has an effect on male or female fertility.

Paediatric population
The safety and efficacy of oseltamivir phosphate for the treatment of influenza in pediatric patients 2 weeks old to 17 years of age has been established.

The safety and efficacy of oseltamivir phosphate for treatment of influenza in pediatric patients less than 2 weeks of age have not been established.

Prophylaxis of Influenza
The safety and efficacy of oseltamivir phosphate for the prophylaxis of influenza in pediatric patients 1 year to 17 years old has been established.

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 phosphate -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 end-stage renal disease (ESRD) undergoing routine hemodialysis or continuous peritoneal dialysis treatment. Oseltamivir phosphate is not recommended for patients with ESRD not undergoing dialysis

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.

Immunocompromised Patients
Efficacy of oseltamivir phosphate for the treatment or prophylaxis of influenza has not been established in immunocompromised patients.

4.7. Effects on Ability to Drive and Use Machines

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

4.8. Undesirable Effects

Tabulated list of adverse reactions
The ARs 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). ARs are added to the appropriate category in the tables according to the pooled analysis from clinical studies.

Table 5: Adverse reactions in studies investigating Oseltamivir phosphate for treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	Common	Uncommon	Rare
Infections and infestations		Bronchitis, Herpes simplex, Nasopharyngitis, Upper respiratory tract infections, Sinusitis		
Blood and lymphatic system disorders				Thrombocytopenia
Immune system disorders			Hypersensitivity reaction	Anaphylactic reactions, Anaphylactoid reactions
Psychiatric disorders				Agitation, Abnormal behaviour, Anxiety, Confusion, Delusions, Delirium, Hallucination, Nightmares, Self-injury
Nervous system disorders	Headache	Insomnia	Altered level of consciousness, Convulsion	
Eye disorders				Visual disturbance
Cardiac disorders			Cardiac arrhythmia	
Respiratory, thoracic and mediastinal disorders		Cough, Sore throat, Rhinorrhea		
Gastrointestinal disorders	Nausea	Vomiting Abdominal pain (incl. upper abdominal pain), Dyspepsia		Gastrointestinal bleedings, 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 (incl. vertigo), Fatigue, Pyrexia, Pain in limb		

Table 6: Adverse reactions in studies investigating Oseltamivir for treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg o.d.])

System Organ Class (SOC)	Adverse reactions according to frequency			
	Very common	Common	Uncommon	Rare
Infections and infestations		Otitis media,		
Nervous system disorders		Headache		
Eye disorders:		Conjunctivitis (including red eyes, eye discharge and eye pain)		
Ear and labyrinth disorders:		Earache	Tympanic membrane disorder	
Respiratory, thoracic and mediastinal disorders	Cough, Nasal congestion	Rhinorrhoea		
Gastrointestinal disorders	Vomiting	Abdominal pain (incl. upper abdominal pain), Dyspepsia, Nausea		
Skin and subcutaneous tissue disorders			Dermatitis (including allergic and atopic dermatitis)	

Description of selected adverse reactions

Psychiatric disorders and nervous system disorders
Influenza can be associated with a variety of neurologic and behavioural symptoms which can include 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 phosphate 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. These cases include fatal fulminant hepatitis/hepatic failure.

Other special populations
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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

Adverse reactions reported following overdose were similar in nature to those observed with therapeutic doses of Oseltamivir phosphate.

5. PHARMACOLOGICAL PROPERTIES

5.1. Mechanism of action

Oseltamivir is an antiviral drug with activity against influenza virus

5.2 Pharmacodynamic Properties

Pharmacotherapeutic group: Neuraminidase inhibitors
ATC code: J05AH02

Oseltamivir phosphate is a pro-drug of the active metabolite (oseltamivir carboxylate). The active metabolite is a selective inhibitor of influenza virus neuraminidase enzymes, which are glycoproteins found on the virion surface. Viral neuraminidase enzyme activity is important both for viral entry into uninfected cells and for the release of recently formed virus particles from infected cells, and for the further spread of infectious virus in the body.

5.3 Pharmacokinetic Properties

Absorption and Bioavailability
Oseltamivir is absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to oseltamivir carboxylate. At least 75% of an oral dose reaches the systemic circulation as oseltamivir carboxylate and less than 5% of the oral dose reaches the systemic circulation as oseltamivir.

Table 7: Mean (% CV) Pharmacokinetic Parameters of Os eltamivir and Os eltamivir Carboxylate Following Multiple Dos ing of 75 mg Caps ules Twice Daily.

P arameter	Oseltamivir	Oseltamivir Carboxylate
C_{max} (ng/ml)	65	348
$AUC_{0\text{-}12h}$ (nh·h/ml)	112	2719

Plasma concentrations of oseltamivir carboxylate are proportional to doses up to 500 mg given twice daily (about 6.7 times the maximum recommended oseltamivir phosphate dosage). Coadministration with food had 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 (6218 ng·h/mL under fasted conditions and 6069 ng·h/mL under fed conditions) of oseltamivir carboxylate.

Distribution
The volume of distribution (Vss) of oseltamivir carboxylate, following intravenous administration in 24 subjects (oseltamivir phosphate is not available as an IV formulation), ranged between 23 and 26 liters. 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.

Elimination
Absorbed oseltamivir is primarily (>90%) eliminated by conversion to the active metabolite, 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 unchanged in urine. Plasma concentrations of oseltamivir carboxylate declined with a half-life of 6 to 10 hours in most subjects after oral administration.

Metabolism
Oseltamivir is extensively converted to the active metabolite, oseltamivir carboxylate, by esterases located predominantly in the liver. Oseltamivir carboxylate is not further metabolized. Neither oseltamivir nor oseltamivir carboxylate is a substrate for, or inhibitor of, cytochrome P450 isoforms.

Excretion
Oseltamivir carboxylate is eliminated entirely (>99%) by renal excretion. Renal clearance (18.8 L/h) exceeds 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 radiolabeled dose is eliminated in feces.

Specific Populations

Renal Impairment
Administration of 100 mg of oseltamivir phosphate 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.

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 Cmin (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 Cmin in patients with normal renal function receiving the approved regimen of 75 mg once daily (40 ng/mL).

Hepatic Impairment
Oseltamivir carboxylate exposure was not altered with mild or moderate hepatic impairment.

Pregnant Women
Oseltamivir phosphate dosage regimen resulted in lower exposure to the active metabolite in pregnant women compared to non-pregnant women. However, this predicted exposure is expected to have activity against susceptible influenza virus strains and there are insufficient pharmacokinetics and safety data to recommend a dose adjustment for pregnant women.

Pediatric (1 year to 12 years of age)
The pharmacokinetics of oseltamivir in pediatric over 12 years of age are similar to those in adult subjects.

Pediatric (2 weeks to less than 1 year of age)
Oseltamivir and oseltamivir carboxylate exposure following a 3 mg/kg dose in pediatrics under 1 year of age is expected to be within the observed exposures in adults and adolescents receiving 75 mg twice daily and 150 mg twice daily.

Geriatric Patients
Dose adjustments are not required for geriatric patients for either treatment or prophylaxis.

Drug Interaction
Oseltamivir is extensively converted to oseltamivir carboxylate by esterases, located predominantly in the liver. Drug interactions involving competition for esterases have not been extensively reported in literature. Low protein binding of oseltamivir and oseltamivir carboxylate suggests that the probability of drug displacement interactions is low. Neither oseltamivir nor oseltamivir carboxylate is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases.

Co-administration of probenecid results in an approximate two-fold increase in exposure to oseltamivir carboxylate due to a decrease in active anionic tubular secretion in the kidney. However, due to the safety margin of oseltamivir carboxylate, no dose adjustments are required when co-administering with probenecid.

No clinically relevant pharmacokinetic interactions have been observed when co-administering oseltamivir with amoxicillin, acetaminophen, aspirin, cimetidine, antacids (magnesium and aluminum hydroxides and calcium carbonates), rimantadine, amantadine, or warfarin.

Microbiology

Mechanism of Action
Oseltamivir phosphate is an ethyl ester prodrug requiring ester hydrolysis for conversion to the active form, oseltamivir carboxylate. Oseltamivir carboxylate is an inhibitor of influenza virus neuraminidase affecting release of viral particles. The median IC50 values of oseltamivir against influenza A/H1N1, influenza A/H3N2, and influenza B clinical isolates were 2.5 nM (range 0.93 to 4.16 nM, N=74), 0.96 nM (range 0.13 to 7.95 nM, N=774), and 60 nM (20 to 285 nM, N=256), respectively, in a neuraminidase assay with a fluorescently labeled MUNANA substrate.

Antiviral Activity
The antiviral 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 influenza virus in cell culture were highly variable depending on the assay method used and the virus tested. The 50% and 90% effective concentrations (EC50 and EC90) were in the range of 0.0008 micromolar to greater than 35 micromolar and 0.004 micromolar to greater than 100 micromolar, respectively (1 micromolar=0.284 microgram per mL). The relationship between the antiviral activity in cell culture, inhibitory activity in the neuraminidase assay, and the inhibition of influenza virus replication in humans has not been established.

Resistance
Cell culture studies: 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.

Clinical studies: Reduced susceptibility isolates have been obtained during treatment with oseltamivir and from sampling during community surveillance studies. The clinical impact of this reduced susceptibility is unknown.

Hemagglutinin (HA) substitutions selected in cell culture and associated with reduced susceptibility to oseltamivir include (influenza virus subtype-specific numbering) A11T, K173E, 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.

Table 4: Neuraminidas e amino acid substitutions associated with reduced susceptibility to Oseltamivir:

Amino acid Substitutions*
Influenza A N1 (N1 numbering in brackets)
I117V (I117V), E119V (E119V), R152K (R152K), Y155H (Y155H), F173V (F174V), D198G/N (D199G/N), I222K/R/T/V (I223K/R/T/V), S246G/N (S247G/N), G248R+I266V (G249R+I267V), H274Y (H275Y), N294S (N295S), Q312R+I427T (Q313R+I427T), N325K (N325K), R371K (R368K)
Influenza A N2
E41G, E119I/V, D151V, I222L/V, Q226H, SASG245-248 deletion, S247P, R292K, N294S
Influenza B (B numbering in brackets)
E119A (E117A), P141S (P139S), G142R (G140R), R152K (R150K), D198E/N/Y (D197E/N/Y), I222L/T/V (I221L/T/V), A246D/S/T (A245D/S/T), H274Y (H273Y), N294S (N294S), R371K (R374K), G402S (G407S)
* All numbering is N2, except where indicated

Selection of influenza A viruses resistant to oseltamivir can occur at higher frequencies in children. Oseltamivir treatment-associated resistance in pediatric treatment studies has been detected at frequencies of 27 to 37% and 3 to 18% (3/11 to 7/19 and 1/34 to 9/50 post-treatment isolates, respectively) for influenza A/H1N1 virus and influenza A/H3N2 virus, respectively.

In immunocompromised adults and pediatrics (1 year of age and older), selection of influenza viruses resistant to oseltamivir can occur at higher frequencies than in the otherwise healthy population. In a treatment study of immunocompromised subjects, treatment-associated genotypic resistance was detected in 27% (8/30), 12% (6/52), and 0% (0/42) of influenza A/H1N1, A/H3N2, and B virus infections, respectively. Treatment-emergent resistance was observed at a higher frequency in hematopoietic stem cell transplant recipients (32%; 6/19).

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

Circulating seasonal influenza strains expressing neuraminidase resistance-associated substitutions have been observed in individuals who have not received oseltamivir treatment. The oseltamivir resistance associated substitution H275Y was found in more than 99% of US-circulating 2008 H1N1 influenza virus isolates. The 2009 H1N1 influenza virus ("swine flu") was almost uniformly susceptible to oseltamivir; however, the frequency of circulating resistant variants can change from season to season. Prescribers should consider available information from the CDC on influenza virus drug susceptibility patterns and treatment effects when deciding whether to use oseltamivir phosphate.

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 virus neuraminidase, 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 virus neuraminidase, confer reduced susceptibility to both oseltamivir and zanamivir. These examples do not represent an exhaustive list of cross-resistance-associated substitutions and prescribers should consider available information from the CDC on influenza drug susceptibility patterns and treatment effects when deciding whether to use oseltamivir phosphate.

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
Treatment with oseltamivir phosphate did not impair normal humoral antibody response to infection.

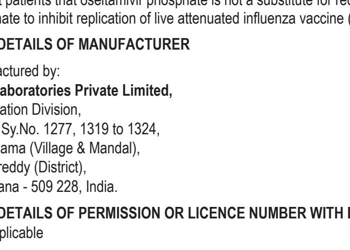
6. NONCLINICAL PROPERTIES

6.1 Carcinogenes is, Mutagenes is, Impairment of Fertility

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. **[Reference: Oseltamivir phosphate. USFDA PI, Dated December 2019]**

7. 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 C16H28N2O4 (free base). The molecular weight is 312.4 for oseltamivir free base and 410.4 for oseltamivir phosphate salt. The structural formula is as follows:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None

8.2 Packing Information

10's PVC/PE/PVDC-Alu Blister Pack

8.3 Storage and Handling Instructions

Do not store above 30⁰C.

9. PATIENT COUNSELLING INFORMATION

Advise the patient to read package insert.

Serious Skin/Hypersensitivity Reactions
Advise patients and/or caregivers of the risk of severe allergic reactions (including anaphylaxis) or serious skin reactions. Instruct patients and/or caregiver to stop oseltamivir phosphate and seek immediate medical attention if an allergic-like reaction occurs or is suspected.

Neuropsychiatric Events
Advise patients and/or caregivers of the risk of neuropsychiatric events in oseltamivir phosphate-treated patients with influenza and instruct patients to contact their physician if they experience signs of abnormal behavior while receiving oseltamivir phosphate.

Important Dosing Information
Instruct patients to begin treatment with oseltamivir phosphate as soon as possible from the first appearance of flu symptoms, within 48 hours of onset of symptoms. Similarly, instruct patients to start taking oseltamivir phosphate for prevention as soon as possible after exposure. Instruct patients to take any missed doses as soon as they remember, except if it is near the next scheduled dose (within 2 hours), and then continue to take oseltamivir phosphate at the usual times.

Influenza Vaccines
Instruct patients that oseltamivir phosphate is not a substitute for receiving an annual flu vaccination. Patients should continue receiving an annual flu vaccination according to guidelines on immunization practices. Because of the potential for oseltamivir phosphate to inhibit replication of live attenuated influenza vaccine (LAIV) and possibly reduce efficacy of LAIV, avoid administration of LAIV within 2 weeks or 48 hours after oseltamivir phosphate administration, unless medically necessary.

10. DETAILS OF MANUFACTURER

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.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Not Applicable

12. DATE OF REVISION

March-2020

D03796-00