For the Use Only of a Registered Medical Practitioner

PRESCRIBING INFORMATION

FLUHALT CAPSULES
(Oseltamivir Phosphate Capsules 75 mg)

COMPOSITION

Each hard gelatin capsule contains: Oseltamivir Phosphate equivalent Oseltamivir…….75 mg

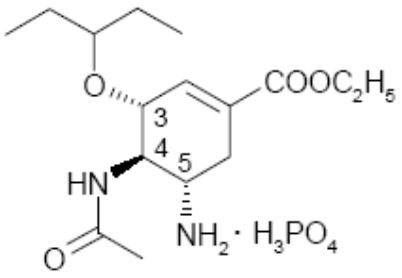
Excipients: Croscarmellose Sodium, Povidone, Pregelatinized Starch, Talc Purified, Sodium Stearyl Fumarate, Purified Water.

PRODUCT DESCRIPTION

Size '2' capsule with yellow cap and light grey body printed in blue ink with OS 75 on both cap and body, containing white to off white powder.

DESCRIPTION

FLUHALT CAPSULES contain oseltamivir phosphate which has 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. The structural formula is as given below:



OSELTAMIVIR PHOSPHATE

INDICATIONS

Treatment of influenza

Oseltamivir is indicated for the treatment of influenza in children 6 to 12 months of age during a pandemic influenza outbreak.

Oseltamivir is indicated for the treatment of influenza in adults and children ≥ 1 year of age.

Treatment should commence as soon as possible but no later than forty-eight hours after the onset of the initial symptoms of infection.

Prophylaxis of influenza

Oseltamivir is indicated for post exposure prophylaxis in adults and children ≥1 year of age following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

DOSE AND METHOD OF ADMINISTRATION

FLUHALT CAPSULES 75 MG (Oseltamivir Capsules 75 mg) may not be suitable for all dosages and therefore, other suitable available strengths and/or dosage forms (e.g. suspension) of oseltamivir should be used in such cases.

Oseltamivir may be taken with or without food. However, oseltamivir taken with food may enhance tolerability in some patients.

During situations when commercially manufactured oseltamivir oral suspension is not readily available, adults, adolescents or children who are unable to swallow capsules, may receive appropriate doses of oseltamivir by opening the capsule providing recommended dosage and pouring the contents of capsule into a suitable, small amount (1 teaspoon maximum) of sweetened food product such as regular or sugar-free chocolate syrup, honey (only for children two years or older), light brown or table sugar dissolved in water, dessert toppings, sweetened condensed milk, apple sauce or yogurt to mask the bitter taste. The mixture should be stirred and the entire contents given to the patient. The mixture must be swallowed immediately after its preparation.

Standard dosage

Treatment of influenza

Treatment should begin within the first or second day of onset of symptoms of influenza.

Adults and adolescents ≥13 years of age

The recommended oral dose of oseltamivir capsules in adults and adolescents ≥13 years of age is a 75 mg capsule twice daily, for 5 days. Adults and adolescents ≥13 years of age that are unable to swallow capsules may receive a dose of 75 mg oseltamivir b.i.d. for 5 days from other available suitable dosage forms (e.g. suspension).

Children ≥1 year of age

Children weighing > 40 kg who are able to swallow capsules, may receive treatment with a 75 mg capsule twice daily.

The recommended oral dose of oseltamivir for children ≥1 year of age is:

Body Weight	Recommended dose for 5 days
15 kg	30 mg twice daily
> 15 kg to 23 kg	45 mg twice daily
> 23 kg to 40 kg	60 mg twice daily
> 40 kg	75 mg twice daily

The recommended oral dose of oseltamivir for infants 6 to 12 months of age

Based on limited PK data currently available, a dosage of 3 mg/kg twice daily in children 6 to 12 months of age, provides plasma exposure to the active metabolite in the majority of patients similar to that shown to be clinically efficacious in older children and adults.

Prophylaxis of influenza

Adult and adolescents ≥13 years of age

The recommended oral dose of oseltamivir for prophylaxis of influenza following close contact with an infected individual is 75 mg once daily for 10 days. Therapy should begin within two days of exposure.

The recommended dose for prophylaxis during a community outbreak of influenza is 75 mg once daily. Safety and efficacy have been demonstrated for up to six weeks. The duration of protection lasts for as long as dosing is continued.

Children ≥ 1 year of age

Children weighing > 40 kg, who are able to swallow capsules, may receive prophylaxis with a 75 mg capsule once daily, for 10 days.

The recommended prophylactic oral dose of oseltamivir for children ≥1 year of age is:

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

Special dosage instructions in special populations

Patients with renal impairment

Treatment of influenza

No dose adjustment is necessary for patients with creatinine clearance above 60 ml/min.

In patients with a creatinine clearance of >30 to 60 ml/min, it is recommended that the dose be reduced to 30 mg of oseltamivir twice daily for 5 days.

In patients with a creatinine clearance of 10 to 30 ml/min, it is recommended that the dose be reduced to 30 mg of oseltamivir once daily for 5 days.

In patients undergoing routine hemodialysis, an initial dose of 30 mg of oseltamivir can be administered prior to the start of dialysis, if influenza symptoms develop during the 48 hours between dialysis sessions. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every hemodialysis session.

For peritoneal dialysis, a dose of 30 mg of oseltamivir administered prior to the start of dialysis followed by further 30 mg doses administered every 5 days is recommended for treatment.

The pharmacokinetics of oseltamivir have not been studied in patients with 'end-stage renal disease' (i.e., creatinine clearance of <10 ml/min) not undergoing dialysis. Hence, dosing recommendation can not be provided for this group.

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

Prophylaxis of influenza

No dose adjustment is necessary for patients with creatinine clearance above 60 ml/min.

In patients with a creatinine clearance of >30 to 60 ml/min, it is recommended that the dose be reduced to 30 mg of oseltamivir once daily.

In patients with creatinine clearance between 10 and 30 ml/min receiving oseltamivir, it is recommended that the dose be reduced to 30 mg of oseltamivir every other day.

In patients undergoing routine hemodialysis, an initial dose of 30 mg of oseltamivir can be administered prior to the start of dialysis. To maintain plasma concentrations at a therapeutic level, a dose of 30 mg should be administered after every alternate hemodialysis session.

For peritoneal dialysis, an initial dose of 30 mg of oseltamivir administered prior to the start of dialysis followed by further 30 mg doses administered every 7 days is recommended for prophylaxis.

The pharmacokinetics of oseltamivir have not been studied in patients with 'end-stage renal disease' (i.e., creatinine clearance of <10 ml/min) not undergoing dialysis. Hence, dosing recommendation can not be provided for this group.

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

Patients with hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic dysfunction in the treatment or prophylaxis of influenza .The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied. No studies have been carried out in pediatric patients with hepatic disorder.

Immunocompromised patients

Seasonal prophylaxis in immunocompromised patients ≥1 year of age and older is recommended for 12 weeks. No dose adjustment is necessary.

Elderly

No dose adjustment is required for elderly patients in the treatment or prophylaxis of influenza, unless there is evidence of moderate or severe renal impairment.

Children

Limited pharmacokinetic data suggest that a dosage of 3 mg/kg twice daily in children 6 to 12 months of age provides plasma exposure to the active metabolite in the majority of patients similar to that shown to be clinically efficacious in older children and adults. Insufficient clinical data are available for recommendation of a dose in children under 6 months of age.

USE IN SPECIAL POPULATIONS

Pregnancy

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

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

Breast-feeding / Lactation

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

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. No studies have been carried out in pediatric patients with hepatic disorder.

Renal impairment

Dose adjustment is recommended for adults with moderate or severe renal impairment (see DOSE AND METHOD OF ADMINISTRATION). There is insufficient clinical data available in children with renal impairment to be able to make any dosing recommendation.

Elderly

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

CONTRAINDICATIONS

FLUHALT CAPSULES (Oseltamivir Capsules) are contraindicated in patients with hypersensitivity to oseltamivir or to any of the components / excipients of the product/formulation. Severe allergic reactions have included anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme.

WARNINGS AND PRECAUTIONS

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.

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 prophylaxisshould 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.

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Oseltamivir has not been shown to prevent such complications.

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.

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.

Pediatric population

No data allowing a dose recommendation for premature children (< 37 weeks post-menstrual age*) are currently available.
* Time between first day of last normal menstrual period and day of assessment, gestational age plus post-natal age.

Serious skin and hypersensitivity reactions

Cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme have been reported in postmarketing experience with oseltamivir. Oseltamivir should be stopped and appropriate treatment instituted if an allergic-like reaction occurs or is suspected.

Renal impairment

Dose adjustment is recommended for both treatment and prevention in adults with moderate or severe renal insufficiency. There is insufficient clinical data available in children with renal impairment to be able to make any dosing recommendation (see DOSE AND METHOD OF ADMINISTRATION; and PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES: Pharmacokinetics).

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 (see UNDESIRABLE EFFECTS).

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. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury, and in some cases resulting in fatal outcomes, in patients with influenza who were receiving oseltamivir. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made but they appear to be uncommon based on oseltamivir usage data. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of oseltamivir to these events has not been established. Closely monitor patients with influenza for signs of abnormal behavior. If neuropsychiatric symptoms occur, evaluate the risks and benefits of continuing treatment for each patient.

Effects on ability to drive and use machines

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

Information for patients

Patients and/or caregivers should be advised of the risk of severe allergic reactions (including anaphylaxis) or serious skin reactions, and should stop oseltamivir and seek immediate medical attention if an allergic-like reaction occurs or is suspected.

Patients and/or caregivers should be advised of the risk of neuropsychiatric events in patients with influenza and should contact their physician if they experience signs of abnormal behavior while receiving oseltamivir. Their physician will determine if oseltamivir treatment should be continued.

Instruct patients to begin treatment with oseltamivir as soon as possible from the first appearance of flu symptoms. Similarly, prevention should begin as soon as possible after exposure, at the recommendation of a physician.

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 at the usual times.

Oseltamivir is not a substitute for a flu vaccination. Patients should continue receiving an annual flu vaccination according to guidelines on immunization practices.

DRUG INTERACTIONS

Pharmacokinetic properties of oseltamivir, such as low protein binding and metabolism independent of the CYP450 and glucuronidase systems (see PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES: Pharmacokinetics), suggest that clinically significant drug interactions via these mechanisms are unlikely.

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. *In vitro* studies demonstrate that neither oseltamivir nor oseltamivir carboxylate is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases.

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.

Additional information: :No pharmacokinetic interactions have been observed when coadministering oseltamivir with acetaminophen, aspirin, cimetidine, antacids (magnesium and aluminum hydroxides and calcium carbonates), rimantadine or warfarin (in subjects stable on warfarin and without influenza).

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).

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, live attenuated influenza vaccine should not be administered within 2 weeks before or 48 hours after administration of oseltamivir, unless medically indicated. The concern about possible interference arises from the potential for antiviral drugs to inhibit replication of live vaccine virus. Trivalent inactivated influenza vaccine can be administered at any time relative to use of oseltamivir.

UNDESIRABLE EFFECTS

The following serious adverse reactions are discussed below and elsewhere in this prescribing information:

- Serious skin and hypersensitivity reactions (see WARNINGS AND PRECAUTIONS)
- Neuropsychiatric events (see WARNINGS AND PRECAUTIONS)

In adults/adolescents, the most commonly reported adverse drug reactions (ADRs) were vomiting and nausea when oseltamivir was used for treatment, and nausea when used for prevention. The majority of these ADRs 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 drug 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. Regarding neuropsychiatric disorders, see WARNINGS AND PRECAUTIONS.

Adverse events reported during treatment and prevention of influenza in adults and adolescents

The below given are the most frequent adverse drug reactions (ADRs) reported when oseltamivir was used for treatment and prevention of influenza in adults and adolescents.

Infections and infestations
Common: bronchitis, herpes simplex, nasopharyngitis, pneumonia, upper respiratory tract infections, sinusitis
Blood and lymphatic system disorders
Rare: thrombocytopenia
Immune system disorders
Uncommon: hypersensitivity reactions
Rare: anaphylactic reactions, anaphylactoid reactions
Psychiatric disorders
Rare: agitation, abnormal behaviour, anxiety, confusion, delusions, delirium, hallucination, nightmares, self-injury
Nervous system disorders
Very common: headache
Common: insomnia
Uncommon: altered level of consciousness, convulsion / seizure
Eye disorders
Rare: Visual disturbance
Cardiac disorders
Uncommon: arrhythmia / cardiac arrhythmia.
Respiratory, thoracic and mediastinal disorders

Common: cough, sore throat, rhinorrhoea
Gastrointestinal disorders
Very common: nausea
Common: vomiting, abdominal pain (including upper abdominal pain), dyspepsia, diarrhoea
Rare: gastrointestinal bleedings, haemorrhagic colitis
Hepatobiliary disorders
Uncommon: elevated liver enzymes
Rare: fulminant hepatitis, hepatic failure, hepatitis
Skin and subcutaneous tissue disorders
Uncommon: dermatitis, rash, urticaria, eczema
Rare: angioneurotic oedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
General disorders
Common: pain/aches, dizziness (including vertigo), fatigue, pyrexia, pain in limb.

Adverse events reported during treatment and prevention of influenza in children

Infections and infestations
Common: pneumonia, sinusitis, bronchitis, otitis media
Nervous system disorders
Common: headache
Eye disorders
Common: conjunctivitis (including red eyes, eye discharge and eye pain)
Ear and labyrinth disorders
Common: ear disorder, earache/ ear pain
Uncommon: tympanic membrane disorder
Respiratory, thoracic and mediastinal disorders
Very common: cough, nasal congestion
Common: rhinorrhea, asthma (including aggravated), epistaxis
Gastrointestinal disorders
Very common: vomiting
Common: abdominal pain (including upper abdominal pain), dyspepsia, nausea, diarrhoea
Skin and subcutaneous tissue disorders
Common: dermatitis (including allergic and atopic dermatitis)
Disorders of the blood and lymphatic system
Common: lymphadenopathy.

Additional adverse events reported during use of oseltamivir includes, unstable angina, anemia, pseudomembranous colitis, humerus fracture, peritonsillar abscess, swelling of the face or tongue, allergy, hypothermia, aggravation of diabetes.

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 pediatric 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 liver function tests abnormal / elevated liver enzymes in patients with influenza-like illness. These cases include fatal fulminant hepatitis/hepatic failure.

Other special populations

Pediatric population (infants less than one year of age)
Safety information available on oseltamivir administered for treatment of influenza in infants less than one year of age suggest that the safety profile in infants less than one year of age is similar to the established safety profile of children aged one year and older.

Elderly patients and patients with chronic cardiac and/or respiratory disease
The population included in the influenza treatment was 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.

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.

OVERDOSE

Reports of overdoses with oseltamivir have been received from reported 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 (see UNDESIRABLE EFFECTS). The anticipated manifestations of acute overdose would be nausea, with or without accompanying vomiting, and dizziness. Patients should discontinue the treatment in the event of overdose. No specific antidote is known.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamics / Mechanism of action

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

Oseltamivir carboxylate has been reported to inhibit influenza A and B neuraminidases. Oseltamivir phosphate has been reported to inhibit influenza virus infection and replication. Oseltamivir given orally has been reported to inhibit influenza A and B virus replication and pathogenicity.

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

Natural mutations associated with reduced susceptibility to oseltamivir have been reported in influenza A and B viruses isolated from patients without exposure to oseltamivir. Immunocompromised patients and young children have been reported to be at a higher risk of developing oseltamivir-resistant virus during treatment.

Pharmacokinetics

General information

Absorption
Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted by predominantly hepatic esterases to the active metabolite (oseltamivir carboxylate). At least 75% of an oral dose reaches the systemic circulation as the active metabolite. Exposure to the pro-drug is less than 5% relative to the active metabolite. Plasma concentrations of both pro-drug and active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution
The mean volume of distribution at steady state of the oseltamivir carboxylate is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. Since neuraminidase activity is extracellular, oseltamivir carboxylate distributes to all sites of influenza virus spread.

The binding of the oseltamivir carboxylate to human plasma protein is negligible (approximately 3%).

Metabolism
Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In vitro* studies demonstrated that neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugates of either compound have been identified *in vivo*.

Elimination
Absorbed oseltamivir is primarily (> 90%) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most subjects. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18.8 L/h) exceeds glomerular filtration rate (7.5 L/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20% of an oral radiolabelled dose is eliminated in faeces.

Special populations

Renal impairment

Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see DOSE AND METHOD OF ADMINISTRATION section.

Hepatic impairment

In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see DOSE AND METHOD OF ADMINISTRATION).

Elderly

Exposure to the active metabolite at steady state was 25 to 35% higher in elderly (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in the elderly were similar to those seen in young adults. On the basis of drug exposure and tolerability, dosage adjustments are not required for elderly patients unless there is evidence of moderate or severe renal impairment (see DOSE AND METHOD OF ADMINISTRATION).

Children

Infants and children 1 year of age or older: Younger children have been reported to clear both the pro-drug and its active metabolite faster than adults, resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg have been reported to give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older have been reported to be similar to those in adults.

STORAGE
Store below 30°C, protected from moisture.

KEEP OUT OF REACH OF CHILDREN.

PACKING
Blister pack of 10's/Box; Box of 10x10's (Not all presentations are available).

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MANUFACTURED BY AND PRODUCT REGISTRATION HOLDER:

Ranbaxy (Malaysia) Sdn. Bhd.

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