Pregnancy and Lactation:

Pregnancy

Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations, including congenital heart defects. A large amount of data on oseltamivir exposure of pregnant women from post-marketing reports and observational studies (more than 1000 exposed outcomes during the first trimester) indicate no malformative nor feto/neonatal toxicity by oseltamivir.

The use of Osmivir 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.

Breastfeeding

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 breastfeeding woman, administration of oseltamivir may be considered, where there are clear potential benefits to breastfeeding mothers.

Side Effects:

In adults/adolescents, the most commonly reported adverse reactions (ARs) were nausea and vomiting in the treatment studies, and nausea in the prevention studies. . The majority of these ARs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days.

In children, the most commonly reported adverse reaction was vomiting. In the majority of patients, these ARs did not lead to discontinuation of OSMIVIR.

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.

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.

Treatment and prevention of influenza in adults and adolescents:
In adult/adolescent treatment and prevention studies, ARs that occurred the most frequently at the recommended dose [75 mg bid for 5 days for treatment and 75 mg od for up to 6 weeks for prophylaxis] are shown in Table 1.

The safety profile reported in subjects who received the recommended dose of OSMIVIR 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.

Table 1: Adverse reactions in adults and adolescents

System Organ Class (SOC)	Adverse reaction according to frequency			
	Very Common	Common	Uncommon	Rare
Infections and Infestations		Brochitis, Herpes simplex, Nasopharyngitis, Upper respiratory tract infection, Sinusitis.		
Blood and lymphatic system				Thrombocytopenia
Immune system disorder			Hypersensitivity reaction	Anaphylactic reactions, Anaphylactoid reactions.
Psychiatric disorder				Agitation,Abnormal behaviour, Anxiety,Confusion,Delusions, Delirium,Hallucination,Nightmares, Self-

Nervous system disorder	Headache	Insomnia	Altered level of consciousness, Convulsion.	
Eye disorder				Visual disturbance
Cardiac disorder			Cardiac arrhythmia	
Respiratory, thoracic and mediastinal disorders		Cough, Sore throat, Rhinorrhea		
Gastrointestinal disorders	Nausea	Vomitting Abdominal pain (incl. upper abdominal pain), Dyspepsia.		Gastrointestinal bleedings, Haemorrhagic colitis.
Hepatobiliary disorders			Elevated liver enzymes	Fulminant hepati -tis, 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		
Infections and infestations		Otitis media		
Nervous system disorders		Headache		
Eye disorders		Conjunctivitis (incl. red eye discharge and eye pain)		
Ear and labyrinth disorders		Earache	Tympanic membrane	
Respiratory, thoracic and mediastinal disorders	Cough, Nasal congestion	Rhinorrhoea		
Gastrointestinal disorders	Vomitting	Abdominal pain (incl. upper abdominal pain, Dyspepsia, Nausea		
Skin and subcutaneous tissue disorders			Dermatitis (incl. allergic and atopic dermatitis)	

Symptoms and Treatment of Overdose:

Adverse events reported following overdose were similar in nature and distribution to those observed with therapeutic doses of OSMIVIR, describes in Undesireable effects. No specific anditode is known.

Contraindications

OSMIVIR is contraindicated in patients with known hypersensitivity to oseltamivir phosphate or to any of the excipients.

Effect on Ability to Drive and Use Machine:

Osmivir has no influence on the ability to drive and use machines

Storage Condition:

Store in a dry place (below 30◦c). Protect from light

Pack Size:

Blister pack of 1 x 10's, 3 x 10's and 5 x 10's.

Product Registration Number:

MAL06100581AZ

Further information can be obtained from your doctor or pharmacist.

ROYCE®

Product Holder/ Manufactured by :
ROYCE PHARMA MFG SDN. BHD. 650435-X
PT1663, Nilai Industrial Estate
71800 Nilai, Negeri Sembilan Darul Khusus, Malays' .

RPI 0096-7

Revision Date: 291025

ROYCE® OSMIVIR CAPSULE 75MG

Presentation:

Size '2' capsules with opaque yellow coloured cap and opaque white coloured body containing white to off white granule.

Content:

Each capsule contains Oseltamivir phosphate equivalent to Oseltamivir 75mg.

Pharmacological Information:

Oseltamivir is a prodrug of oseltamivir carboxylate, an inhibitor of the enzyme neuraminidase (sialidasee) which has a role in the infectivity and replication of influenza A and B viruses. It is used for the treatment and postexposure prophylaxis of influenza A and B, including pandemic strains.

Pharmacokinetics:

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 inflenza virus spread. The binding of the oseltamivir carboxylate to human plasma protein is neglible (approximately 3 %).

Biotransformation

Oseltamivir is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. In vitro studies demonstrated that neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms. No phase 2 conjugate 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 concentration 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.

Indication:

Treatment of influenza:

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

Prevention of influenza:

OSMIVIR is indicated for post exposure prevention in adults and children > 1 year following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community.

Dosage and Administration:

Adults, adolescents 13 years and over

Treatment:

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

Body Weight (kg)	Recommended Dose for 5 days	Recommended Dose for 10 days*
> 40	75 mg twice daily	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 (13 to 17 years of age) and adults.

Body Weight (kg)	Recommended Dose for 5 days	Recommended Dose for 10 days*
> 40	75 mg once daily	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 (or up to 12 weeks in immunocompromised patients).

Paediatric population

Children 1 to 12 years of age

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

Treatment:

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

Body Weight (kg)	Recommended Dose for 5 days	Recommended Dose for 10 days*
10 - 15	30 mg twice daily	30 mg twice daily
> 15 - 23	45 mg twice daily	45 mg twice daily
> 23 - 40	60 mg twice daily	60 mg twice daily
> 40	75 mg twice daily	75 mg twice daily

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

Post-exposure prevention

The recommended post-exposure prevention dose of OSMIVIR is:

Body Weight (kg)	Recommended Dose for 5 days	Recommended Dose for 10 days*
10 - 15	30 mg once daily	30 mg once daily
> 15 - 23	45 mg once daily	45 mg once daily
> 23 - 40	60 mg once daily	60 mg once daily
> 40	75 mg once daily	75 mg once daily

Prevention during an influenza epidemic in the community:

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

Infants 6-12 months of age

Treatment

The recommended treatment dose for infants 6- 12 months of age is 3 mg/kg twice daily. The following dosing regimen is recommended for treatment of infants 6 – 12 months of age:

Body Weight (kg)	Recommended Dose for 5 days	Recommended Dose for 10 days*
3	9 mg twice daily	9 mg twice daily
4	12 mg twice daily	12 mg twice daily
5	15 mg twice daily	15 mg twice daily
6	18 mg twice daily	18 mg twice daily
7	21 mg twice daily	21 mg twice daily
8	24 mg twice daily	24 mg twice daily
9	27 mg twice daily	27 mg twice daily
10	30 mg twice daily	30 mg twice daily

This table is not intended to contain all possible weights for this population. For all patients under the age of 1 year, 3 mg/kg should be used to determine dose regardless of the weight of the patient.
Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.
***Immunsnicompromised Patients.**
**** The recommended duration in immunocompromised infants (6-12 months old) is 10 days**

This dosing recommendation is not intended for premature infants, i.e. those with a post-conceptual age less than 36 weeks. Insufficient data are available for these patients, in whom different dosing may be required due to the immaturity of physiological functions.

Special Populations

Hepatic impairment

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

Renal impairment:

Treatment of Influenza

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

Creatinine Clearance (ml/min)	Recommended dose for Treatement
< 10	Not recommended (no data available)
> 10 to 30	30 mg (suspension/ capsule) once daily
> 30 to 60	30 mg (suspension/ capsule) twice daily
> 60	75 mg twice daily
Haemodialysis patients	30 mg suspension after each session
Peritoneal dialysis patients	30 mg (suspension/ capsule) single dose

Prevention of Influenza

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

Creatinine Clearance (ml/min)	Recommended dose for Treatement
< 10	Not recommended (no data available)
> 10 to 30	30 mg (suspension/ capsule) every second day daily
> 30 to 60	30 mg (suspension/ capsule) once daily
> 60	75 mg once daily
Haemodialysis patients	30 mg after every second session
Peritoneal dialysis patients	30 mg (suspension/ capsules) 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.**

Elderly

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

Immunocompromised patients

Treatment

The recommended duration for immunocompromised patients is 10 days . No dose adjustment is necessary. 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.

Warning 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.

OSMIVIR is not a substitute for influenza vaccination. Use of OSMIVIR must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as OSMIVIR is administered. OSMIVIR should be used for the treatment and prevention of influenza only when reliable epidemiological data indicate that influenza virus is circulating in the community.

This preparation contains Tartrazine / FD & C Yellow No.5 / MA Yellow A-2 / Aluminic Lake that may cause allergic reactions in certain susceptible patients.

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.

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.

Neuropsychiatric events

Neuropsychiatric events have been reported during administration of OSMIVIR 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.

Interactions with other medicaments :

Osmivir may have potentially inhibit replication of the influenza virus in live influenza virus vaccines. Therefore, US licensed product information states that live influenza virus vaccines should not be given until 48 hours after stopping Osmivir and that Osmivir should not be given for 2 weeks after live influenza virus vaccines have been given, Inactivated (split virion or surface antigen) vaccines are not expected to be affected by Osmivir.

Antiviral Action

Oseltamivir has antiviral activity similar to that of zanamivir. Its active metabolite, oseltamivir carboxylate, selectively blocks the viral surface enzyme neuraminidase, thereby preventing the release of virus particles from infected cells. Oseltamivir is active against influenza A and B viral neuraminidase.

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, acetylsalicylic acid, cimetidine, antacids (magnesium and aluminium hydroxides and calcium carbonates), rimantadine or warfarin (in subjects stable on warfarin and without influenza).