APPROVED PROFESSIONAL INFORMATION FOR OZELET

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

OZELET 6 mg/mL powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 6 mg oseltamivir equivalent to 7,882 mg of oseltamivir.

phosphate after constitution.

Contains sugar “sorbitol and saccharin sodium”.

OZELET**:** contains 173,128 mg sorbitol.

OZELET**:** contains 0,640 mg Saccharin sodium.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for oral suspension

White to pale yellow, tutti-frutti flavored granular or clumped granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment:

OZELET is indicated for the treatment of influenza in adults and children ≥ 1 year of age (see section 4.4 and section 4.2).

PANDEMIC USE:

OZELET is indicated for the treatment of infants 6-12 months of age during a pandemic influenza outbreak only, and not for endemic (seasonal) influenza use, (see section 4.4 and

section 5.2)

PROPHYLAXIS:

OZELET is indicated for the prophylaxis of influenza in adults and children ≥ 1 year of age.

4.2 Posology and method of administration

Posology

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 who are unable to swallow capsules may receive a dose of 75 mg **OZELET** powder for oral suspension twice daily, for 5 days.

Children:

The recommended oral dose of ***OZELET*** *powder for oral suspension for children ≥ 1 year of age is:*

Body weight	***Recommended treatment dose for 5 days***
	6 mg/mL oral suspension
≤15 kg	5,0 mL twice daily
> 15 kg to 23 kg	7,5 mL twice daily
> 23 kg to 40 kg	10,0 mL twice daily
> 40 kg	12,5 mL twice daily

A 10 mL oral dosing syringe is provided for the 6 mg/mL oral suspension for children ≥ 1 year of age.

It is recommended that OZELET powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient.

The recommended oral dose of OZELET for children 6 – 12 months of age:

Based on limited pharmacokinetic data currently available, a dosage of 3 mg/kg twice daily in children 6 - 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.

Recommended volumes of reconstituted oral suspension to be drawn up into an oral syringe (3 mg/kg body weight) are shown in the table below:

Body weight (kg)	***OZELET (mg)***	***Rounded volume of 6 mg/mL suspension***
6	18	3 mL

7	21	3,5 mL
8	24	4 mL
9	27	4,5 mL
≥ 10	30	5 mL

Use the smallest graduated oral syringe that will accurately deliver the appropriate volume.

The recommended treatment dose for infants 6 - 12 months is3 mg/kg twice daily for 5 days, during a pandemic influenza outbreak only, and not for endemic (seasonal) influenza use (see section 5.2)

Children ≥ 1 year of age

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

Body weight	***Recommended treatment dose for 10 days***
	6 mg/mL oral suspension
≥15 kg	5,0 mL once daily
> 15 kg to 23 kg	7,5 mL once daily
> 23 kg to 40 kg	10,0 mL once daily
> 40 kg	12,5 mL once daily

A 10 mL oral dosing syringe is provided for the 6 mg/mL oral suspension.

It is recommended that OZELET powder for oral suspension be constituted by a pharmacist prior to dispensing to the patient (see section 6.6)

Special Dosage Instructions

Patients with renal impairment

Treatment of influenza: No dose adjustment is necessary for patients with creatinine clearance above 60 mL/min. In patients a with creatinine of > 30 – 60 mL/min, it is recommended that the treatment dose be reduced to 30 mg of OZELET twice daily for 5 days. In patients with a creatinine clearance of 10 - 30 mL/min, it is recommended that the dose be reduced to 30 mg of OZELET once daily for 5 days. In patients undergoing routine haemodialysis an initial dose of 30 mg OZELET 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 haemodialysis session.

For peritoneal dialysis an initial dose of 30 mg of OZELET administered prior to the start of dialysis followed by further 30 mg doses administered every 5 day s is recommended for treatment(see section 5.2 and 4.4). The pharmacokinetics of OZELET have not been studied in patients with “endstage renal disease” (i.e. creatinine clearance < 10 mL/min) not undergoing dialysis. Hence, dosing recommendation cannot be provided for this group.

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 - 60 mL/min, it is recommended that the dose be reduced to 30 mg of OZELET once daily. In patients with a creatinine clearance between 10 and 30 mL/min receiving OZELET, it is recommended that the dose be reduced to 30 mg of OZELET every other day. In patients undergoing routine haemodialysis an initial dose of 30 mg of OZELET 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 haemodialysis session. For peritoneal dialysis an initial dose of 30 mg of

OZELET administered prior to the start of dialysis followed by further 30 mg doses administered every 7 days is recommended for prophylaxis (see section 5.2 and 4.~~2~~4). The pharmacokinetics of OZELET have not been studied in patients with"end-stage renal disease" (i.e.,creatinine clearance < 10 mL/min) not undergoing dialysis Hence, dosing recommendation cannot be provided for this group.

Patients with hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic dysfunction in the treatment or prophylaxis of influenza(see 5.2). The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Immuno-compromised patients

Seasonal prophylaxis in immuno-compromised 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 (see section 5.2).

Children

The safety and efficacy of OZELET in children under1 year has not been established (see section 5.2). OZELET should not be used in children under 1 year of age, other than during a pandemic influenza outbreak.

Method of administration

For oral use

OZELET may be taken with or without food. (see section 5.2).

However, **OZELET** taken with food may enhance tolerability in some patients.

4.3 Contraindications

Hypersensitivity to any of the ingredients of OZELET, including the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Neuropsychiatric events such as convulsions, abnormal and inappropriate behaviour,disturbances in consciousness, hallucinations and delirium have been reported during oseltamivir administration in patients with influenza. In some cases, the delirium resulted in accidental self-injury and death. These events occurred mostly within the first few days of taking oseltamivir.

Patients, and especially paediatric and adolescent patients, taking oseltamivir should be carefully monitored for signs of abnormal behaviour, and the benefits and risks of continuing treatment should be carefully evaluated for each patient (see section 4.8).

OZELET is effective only against illness caused by influenza viruses.

There is no evidence for efficacy of OZELET in any illness caused by medicines other than influenza viruses types A and B (see section 5.1).

OZELET is not a substitute for influenza vaccination.

Resistance of influenza viruses to oseltamivir have been reported. The prevalence of virus resistance and virus strains on subtypes differs between countries and seasons. In South Africa where H1N1 viruses predominated among circulating strains, 100 % [225/225] of H1N1 viruses tested in 2008 were resistant to oseltamivir. The resistance of the predominant virus to oseltamivir generally changes from season to season. Updated local surveillance data from the National Institute for Communicable Diseases (NICD) should be consulted for information on seasonal prevalence of medicine resistant viruses.

Based on limited pharmacokinetic and safety data, OZELET may only be used in infants 6 – 12 months of age for treatment during a pandemic influenza outbreak. The treating doctor should take into account the pathogenicity of the circulating strain and the underlying condition of the patient to

ensure that there is a potential benefit to the child.

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 (see section 5.1).

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 (see section 5.1).

Severe renal impairment

Dose adjustment is recommended for both treatment and prevention in adolescents (13-17 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 (see section 4.2 and 5.2).

Dose adjustment is recommended for patients with creatinine clearance of 10 - 60 mL/min for the treatment of influenza and the prophylaxis of influenza.

No dosing recommendation is available for patients undergoing routine haemodialysis and continuous peritoneal dialysis with end stage renal disease and for patients with creatinine clearance of ≤ 10 mL/min (see section 4.2).

OZELET should not be used in children under 1 year of age, other than during a pandemic influenza outbreak.

Excipients

OZELET contains sorbitol. Patients with hereditary fructose intolerance

(HFI) should not take OZELET.

Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

This medicine contains sodium benzoate. Sodium benzoate may increase jaundice in newborn babies (up to 4 weeks old).

Paediatric population

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

4.5 Interaction with other medicines and other forms of interaction

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

Oseltamivir is extensively converted to the active compound by esterases, located predominantly in the liver. Interactions involving competition for esterases have not been extensively reported in the literature.

In vitro studies demonstrated that neither oseltamivir nor the active metabolite is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases, see section 5.2 There is no mechanistic basis for an interaction with oral contraceptives.

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 medicine interactions involving competition for renal tubular secretion are unlikely, due to the known safety margin for most of these medicines, 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 OZELET in patients when taking co- excreted medicines with a narrow therapeutic margin (e.g. chlorpropamide, methothrexate, phenylbutazone).

Additional information

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

No teratogenic effect was not observed in animal reproductive studies. No studies have been conducted with the use of OZELET in pregnant women.

Breastfeeding

Safety in lactation has not been established.

In lactating rats, oseltamivir and the active metabolite are excreted in the milk.

Limited information is available on infants breastfed by mothers taking

oseltamivir and on excretion of oseltamivir in breast milk.

Limited data demonstrated that low levels of oseltamivir and the active metabolite were detected in breast milk.

Safety in humans has not been demonstrated in children of breastfeeding women using OZELET**.**

Mothers on treatment with **OZELET** should not breastfeed their infants.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and use machines

It is not known whether OZELET could affect the ability to drive a car or operate machinery. However, if symptoms such as delirium or fever are experienced while taking OZELET, patients should be advised not drive or use machines until the symptoms disappear.

4.8 Undesirable effects

a) Summary of the safety profiles

In adults/ adolescents, treatment studies the most frequently reported adverse reactions (ARs) were nausea and vomiting and headache. 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 adult/adolescent prophylaxis studies, the most frequently reported adverse reaction were vomiting nausea headache and pain. In children the most frequently reported ADR was vomiting.

The following serious adverse reactions have been reported anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice) angioneutotic oedema, stevens-johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders. (Regarding neuropsychiatric disorders, see section 4.4).

b. Tabulated summary of adverse reactions

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 twice a day for 5 days for treatment and 75 mg once daily for up to 6 weeks for prophylaxis) are shown in Table 1.

The safety profile reported in subjects who received the recommended dose of OZELET 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 studies investigating Tamiflu for treatment and prevention of influenza in adults and adolescents or through post- marketing surveillance

Infections and infestations	
Frequency unknown:	Bronchitis, Herpes simplex, Nasopharyngitis, Upper respiratory tract infections, Sinusitis, Influenza
Blood and lymphatic system disorders	
Less frequent:	Thrombocytopenia

Immune system disorders	
Less frequent:	Hypersensitivity reaction, anaphylactic reactions, anaphylactoid reactions
Psychiatric disorders	
Less frequent:	Agitation, abnormal behaviour, anxiety, confusion, delusions, delirium, hallucination, nightmares, self-injury
Nervous system disorders	
Frequent:	Headache,
Less frequent:	Altered level of consciousness, convulsion
Frequency unknown	Insomnia
Eye disorders	
Less frequent	Visual disturbance
Cardiac disorders	
Less frequent:	Cardiac dysrhythmia
Respiratory, thoracic and mediastinal disorders	
Frequent:	sore throat,
Frequency unknown	Cough, nasal congestion, rhinorrhea
Gastrointestinal disorders	

Frequent:	Nausea, vomiting,
Less frequent:	Gastrointestinal bleedings, haemorrhagic colitis
Frequency unknown	abdominal pain (including upper abdominal pain), diarrhoea, dyspepsia
Hepato-biliary disorders	
Less frequent:	Elevated liver enzymes, fulminant hepatitis, hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	
Less frequent:	Eczema, dermatitis, rash, urticaria, angioneurotic oedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Frequency unknown:	Back pain, arthralgia, myalgia
Reproductive system and breast disorders	
Frequency unknown:	dysmenorrhoea
General disorders and administration site conditions	
Frequent:	Pain
Frequency unknown	dizziness (including vertigo), fatigue,

	pyrexia, pain in limb, influenza-like illness

Treatment and prevention of influenza in children:

Table 2 Adverse reactions of OZELET for treatment and prevention of influenza in children

Infections and infestations	
Frequency unknown:	Otitis media, pneumonia, sinusitis, bronchitis,
Blood and lymphatic system disorders	
Frequency unknown:	Lymphadenopathy
Nervous system disorders	
Frequent:	Headache
Eye disorders	
Frequency unknown:	Conjunctivitis (including red eyes, eye discharge and eye pain)
Ear and labyrinth disorders	
Frequency unknown:	Earache, Tympanic membrane disorder
Respiratory, thoracic and mediastinal disorders	
Frequency unknown:	Cough, nasal congestion, rhinorrhoea, asthma (including aggravated asthma),

	epistaxis
Gastrointestinal disorders	
Frequent:	Vomiting, dyspepsia
Frequency unknown:	diarrhoea, abdominal pain (including upper abdominal pain), nausea
Skin and subcutaneous tissue disorders	
Frequency unknown:	Dermatitis (including allergic and atopic dermatitis)

c. 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 OZELET, there have been post marketing reports of convulsions and delirium (including symptoms such as altered level of consciousness, confusion, abnormal behaviour, delusions, hallucinations, agitation, anxiety, nightmares), in a very few cases resulting in self-injury or fatal outcomes. These events were reported primarily among paediatric and adolescent patients and often had an abrupt onset and rapid resolution. The contribution of oseltamivir to those events is unknown. Such neuropsychiatric events have also been reported in patients with influenza who were not taking oseltamivir.

Immune system disorders: allergy, anaphylactic/anaphylactoid reactions and face oedema have been reported.

Skin and subcutaneous tissue disorders: Cases of hypersensitivity reactions such as allergic skin reactions including dermatitis, rash, eczema, urticaria, erythema multiforme, Stevens-Johnson Syndrome, and toxic epidermal necrolysis have been reported.

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.

Gastrointestinal disorders: Gastrointestinal bleedings, in particular, haemorrhagic colitis was reported that subsided when the course of influenza abated or treatment with oseltamivir was interrupted.

Other special populations

Paediatric population (infants less than one year of age)

In two studies to characterise the pharmacokinetics, pharmacodynamics and safety profile of oseltamivir therapy in influenza infected children less than one year of age, the safety profile was similar among age cohorts with vomiting, diarrhoea and diaper rash being the most frequently reported adverse events (see section 5.2). Insufficient data are available for infants who have a post-conceptual age of less than 36 weeks.

Safety information available on oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies, epidemiological databases research and post marketing reports 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.

Older people and patients with chronic cardiac and/or respiratory disease The population included in the influenza treatment studies is comprised of otherwise healthy adults/adolescents and patients “at risk” (patients at higher risk of developing complications associated with influenza, e.g. older people

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.

Immunocompromised patients

The treatment of influenza in immunocompromised patients were evaluated in two studies receiving standard dose or high dose regimens (double dose or triple dose) of oseltamivir (see section 5.1). The safety profile of oseltamivir observed in these studies was consistent with that observed in previous clinical trials where oseltamivir was administered for treatment of influenza in non-immunocompromised patients across all age groups (otherwise healthy patients or "at risk" patients [i.e., those with respiratory and/or cardiac co-morbidities]). The most frequent adverse reaction reported in immunocompromised children was vomiting (28%). In a 12-week prophylaxis study in immunocompromised patients, including 18 children 1 to 12 years of age and older, the safety profile in patients who received oseltamivir was consistent with that previously observed in oseltamivir prophylaxis clinical studies.

Children with pre-existing bronchial asthma

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/publications/Index/8

4.9 Overdose

In overdose symptoms may be the exacerbation or exaggeration of side effects

Treatment is supportive and symptomatic

No specific antidote is known.

Paediatric population

Overdose has been reported more frequently for children than adults and adolescents. Caution should be exercised when preparing OZELET oral suspension and when administering OZELET to children.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use,

neuraminidase inhibitors ATC code: J05AH02

CATEGORY AND CLASS

A 20.2.8 Antiviral agents

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 is essential for both 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 inhibits influenza A and B neuraminidases in vitro.

Oseltamivir phosphate inhibits influenza virus infection and replication in vitro.

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

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

Neuraminidase enzyme IC50 values for oseltamivir for clinically isolated influenza A ranged from 0,1 nM to 1,3 nM, and for influenza B was 2,6 nM. Higher IC50 values for influenza B, up to a median of 8,5 nM, have been observed in published studies.

Oseltamivir resistance

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

5.2 Pharmacokinetic properties

Absorption

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate (pro-drug) and is extensively converted predominantly by hepatic esterases to the active metabolite (oseltamivir carboxylate). Plasma concentrations of the active metabolite are measurable within 30 minutes, reach exceed near maximal levels in 2 to 3 hours post dose, and substantially (> 20-fold) those of the pro-drug.

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 (see section 4.2)

Distribution

The mean volume of distribution (Vss) of the active metabolite is approximately 23 litres in humans, a volume equivalent to extracellular body fluid. The active moiety reaches all key sites of influenza infection as shown by studies in the ferret, rat and rabbit.

In these studies, antiviral concentrations of the active metabolite were seen in the lung, bronchoalveolar lavage, nasal mucosa, middle ear and trachea following oral administration of doses of oseltamivir phosphate. The binding of the active metabolite to human plasma protein is negligible (approximately 3 %).

The binding of the pro-drug to human plasma protein is 42 %. These levels are insufficient to cause significant medicine interactions.

Biotransformation

Oseltamivir phosphate is extensively converted to the active metabolite by esterases located predominantly in the liver. Neither oseltamivir nor the active metabolite is substrates for or inhibitors of cytochrome P450 isoforms, (see section 4.5)

Elimination

Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to the active metabolite. The active metabolite is not further metabolised and is eliminated in the urine. Peak plasma concentrations of the active metabolite decline, with a half-life of 6-10 hours in most subjects. The active drug 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 in addition to glomerular filtration occurs. Less than 20 % of an oral radio-labelled dose is eliminated in faeces.

Pharmacokinetics in special population

***Patients with renal impairment*:**

Administration of 100 mg of oseltamivir twice daily for five days to patients with various degrees of

renal impairment showed that exposure to the active metabolite is inversely proportional to declining renal function.

***Treatment of influenza*:**

No dose adjustment is necessary for patients with creatinine clearance above 60 mL/min. In patients with a creatinine clearance of 30-60 mL/min, it is recommended that the dose be reduced to 30 mg of oseltamivir once daily for 5 days.

In patients undergoing routine haemodialysis an initial dose of 30 mg of oseltamivir can be administered prior to the start of dialysis in patients with influenza symptoms 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 haemodialysis 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 5 days is recommended for treatment (see section 4.2 and 4.4). 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 cannot be provided for this group.

***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 - 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 haemodialysis 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 haemodialysis 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 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 cannot be provided for this group.

Patients with hepatic impairment

In-vitro studies have shown 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 section 4.2)

The safety and pharmacokinetics in patients with severe hepatic impairment have not been studied.

Elderly

Exposure to the active metabolite at steady state was 25-35 % higher in elderly (age range 65-78) compared to young adults who were given comparable doses observed in the elderly were similar to those seen in young of medicine exposure and tolerability, dosage adjustments are not required for elderly patients for either the treatment or prophylaxis of influenza unless there is evidence of moderate or severe renal Impairment (creatinine clearance below 60 mL/min) (see section 4.2).

Immunocompromised Patients

Population pharmacokinetic analyses indicate that treatment of adult and paediatric (< 18 years old) immunocompromised patients with oseltamivir (as described in section 4.2 results in an increased predicted exposure (from approximately 5 % up to 50 %) to the active metabolite when compared to non-immunocompromised patients with comparable creatinine clearance.

Due to the wide safe margin of the active metabolite, no dose adjustments are required in patients due to their immunocompromised status. However, for immunocompromised patients with renal impairment, doses should be adjusted as outlined in section 4.2.

Pharmacokinetic and pharmacodynamic analyses from two studies in immunocompromised patients indicated that there was no meaningful additional benefit in exposures higher than those achieved after the administration of the standard dose.

Paediatric population

Children ≥ 1 year of age

The pharmacokinetics of oseltamivir has been evaluated in single dose pharmacokinetic studies in children aged 1 to 16 years. Multiple dose pharmacokinetics was studied in a small number of children aged 3-12 years enrolled in a clinical trial. The rate of clearance of the active metabolite, corrected for bodyweight, was faster in children than in adults, resulting in lower exposure in these children for a given mg/kg dose. The rate of clearance of the active metabolite increased with decreasing age over the age 16 years. Doses of 2 mg/kg yield oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg capsule dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children over 12 years of age are similar to those in adults.

Infants 6 to 12 months of age

Limited pharmacokinetic and safety data are available for infants less than 2 years of age. Pharmacokinetic modelling was undertaken using these data in addition to data from studies in adults and children older than 1 year of age.

The results demonstrate that doses of 3 mg/kg twice daily for infants aged 6 to 12 months provide exposures similar to those shown to be clinically efficacious in adults and children > 1 year of age (see section 4.1)

Infants and children 1 year of age or older

The pharmacokinetics of oseltamivir have been evaluated in single-dose pharmacokinetic studies in infants, children and adolescents 1 to 16 years of age. Multiple-dose pharmacokinetics were studied

in a small number of children enrolled in a clinical efficacy study. Younger children cleared both the pro-drug and its active metabolite faster than adults, resulting in a lower exposure for a given mg/kg dose. Doses of 2 mg/kg give oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children and adolescents 12 years of age or older are similar to those in adults.

6. Pharmaceutical particulars

6.1 List of excipients

Oseltamivir phosphate

Sorbitol

Saccharin sodium

Monosodium citrate anhydrous

Dehydrated alcohol

Sodium benzoate

Titanium dioxide

Tutti-frutti Flavor

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light and moisture.

Keep the bottle tightly closed

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

100 ml Amber glass bottle (type-III (SGD)) with a child- resistant plastic caps with Expended PE wad, 28 mm

6.6 Special precautions for disposal and other handling

It is recommended that Powder for Oral Suspension should be reconstituted by the pharmacist prior to its dispensing to the patient.

After reconstitution with 55 ml of water, this usable volume of oral Suspension allows for the retrieval of a total doses of 30 mg Oseltamivir.

Preparation of 6 mg/ml Oral Suspension

To obtain 64,7 ml (60 ml retrievable) of suspension

1.Tap the closed bottle gently several times to loosen the powder.

2. Measure 55 ml of water. Use the measuring cup (where provided) and fill it to the indicated level.

3. Add all 55 ml of water for constitution to the bottle and shake the closed bottle well for 15 seconds.

4. Remove the child-resistant cap and push bottle adapter into neck of bottle.

5. Close bottle with the child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap.

When OZELET Powder for Oral Suspension is not Available.

During situations when commercially manufactured OZELET powder for oral suspension is not readily available, adults, adolescents or children who are unable to swallow capsules may receive appropriate doses of OZELET by opening capsules and pouring the contents

of capsules into a suitable, small amount (1 teaspoon (5 ml) 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 yoghurt 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.

When using the 30 mg and 45 mg capsules: follow these instructions to ensure proper dosing:

1. Determine the number of capsules that are needed to prepare a mixture with this procedure:

Body Weight*	***Recommended number of capsule(s) needed to obtain the recommended doses for 5 days treatment***	***Required number of capsule(s) needed to obtain the recommended doses for prevention (10 days)***
Less than or equal to 15 kg	1 capsule of 30 mg twice daily	1 capsule of 30 mg once daily
More than 15 kg and up to 23 kg	1 capsule of 45 mg twice daily	1 capsule of 45 mg once daily
More than 23 kg and up to 40 kg	2 capsules of 30 mg twice daily	2 capsules of 30 mg once daily

2. Check that the correct dose according to the table above is used. The capsule(s) must be held over a small bowl, carefully pulled open and the powder poured into the bowl.

3. A suitable, small amount (1 teaspoon (5 ml) maximum) of sweetened food product must be added to the bowl (to mask the bitter taste) and the contents well mixed.

4. The mixture must be stirred and the entire contents of the bowl given to the patient.

This mixture must be swallowed by the patient immediately after some mixture left inside the bowl, the bowl must be rinsed with a small amount of water and the patient must drink this remaining mixture.

For patients requiring 30 - 60 mg doses, follow these instructions:

1. One OZELET 75 mg capsule must be held over a the capsule must be carefully pulled open and the powder poured into the small bowl.

2. 5 ml water must be added to the powder using a graduated syringe and the mixture stirred for approximately two minutes.

3. The correct amount of mixture must be drawn up into the syringe from the bowl. See the table below to determine the correct amount of mixture, based on the patient's weight.

It is not necessary to draw up any undissolved white powder as this is inert material.

The plunger of the syringe must be pushed down to empty its entire contents into a second bowl and any unused mixture discarded.

Body weight	***Recommended t dose***	***Required amount of {PRODUCT NAME} mixture for one dose***
Less than or equal to 5 kg	40 mg	2 ml
More than 23 kg and up to 40 kg	45 mg	3 ml
More than 23 kg and up to 40 kg	60 mg	4 ml

4. The recommended dose is 30 mg, 45 mg or 60 mg twice daily for 5 days for treatment, and once daily for prevention for 10 days.

5. In the second bowl, a suitable, small amount (1 teaspoon (5 ml) maximum) of sweetened food product must be added to the mixture (to mask the bitter taste) and well mixed.

6. This mixture must be stirred and the entire contents of the second bowl given to the patient. This mixture must be swallowed immediately after its preparation. If there is some mixture left inside the bowl, the bowl must be rinsed with a small amount of water and the patient must drink this remaining mixture.

For patients requiring 75 mg dose, follow these instructions:

1. One 75 mg capsule must be held over a small bowl, the capsule must be carefully pulled open and the powder poured into the bowl.

2. A suitable, small amount (1 teaspoon (5 ml) maximum) of sweetened food product must be added to the mixture (to mask the bitter taste) and well mixed.

3. The mixture must be stirred and the entire contents of the bowl given to the patient. This mixture must be swallowed immediately after its preparation. If there is some mixture left inside the bowl, it must be rinsed with a small amount of water and the patient must drink this remaining mixture.

Repeat this procedure every time this medicine is taken.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER (S)

OZELET 6 mg/mL:56/20.8/1087

9 DATE OF FIRST AUTHORISATION

10 October 2023

10 DATE OF REVISION OF THE NEXT