PI for MACSELTA 75 mg CAPSULES

SCHEDULING STATUS

1. NAME OF THE MEDICINE

MACSELTA 75 mg CAPSULES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MACSELTA 75 mg CAPSULES

Each capsule contains oseltamivir phosphate equivalent to oseltamivir 75 mg.

Sugar free.

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsule.

MACSELTA 75 mg CAPSULES:

Light yellow cap and grey body size ‘2’ hard gelatin capsule containing white to off white granules with “75 mg” on cap and “M 55” on body imprinted with blue ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TREATMENT:

MACSELTA 75 mg CAPSULES is indicated for the treatment of influenza in adults and children ≥1 year of age.

PANDEMIC USE:

MACSELTA 75 mg CAPSULES 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.

PROPHYLAXIS:

MACSELTA 75 mg CAPSULES 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*:* The recommended oral dose in adults and adolescents ≥13 years is one **MACSELTA 75 mg CAPSULES** twice daily, for 5 days.

Children: Children > 40 kg or ≥ 8 years who are able to swallow capsules, may also receive treatment with one **MACSELTA 75 mg CAPSULES** twice daily.

Prophylaxis of influenza

The recommended oral dose of **MACSELTA 75 mg CAPSULES** for prophylaxis of influenza following close contact with an infected individual is one **MACSELTA 75 mg CAPSULES** once daily for at least 10 days.

Therapy should begin within two days of exposure.

The recommended dose for prophylaxis during a community outbreak of influenza is one **MACSELTA 75 mg CAPSULES** 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 also receive prophylaxis with one **MACSELTA 75 mg CAPSULES** once daily for 10 days.

Special populations:

Patients with renal impairment:

Treatment of influenza

No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with a creatinine clearance of 10-30 mL/min it is recommended that the dose be reduced to 75 mg of

MACSELTA 75 mg CAPSULES once daily for 5 days. 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 ≤ 10mL/min. (See section 5.2 and section 4.4)

Prophylaxis of influenza

No dose adjustment is necessary for patients with creatinine clearance above 30 mL/min. In patients with creatinine clearance between 10 and 30 mL/min receiving **MACSELTA 75 mg CAPSULES** it is recommended that the dose be reduced to 75 mg of **MACSELTA 75 mg CAPSULES** every other day.

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 ≤10 mL/min. (See section 5.2 and section 4.4)

Patients with hepatic impairment:

No dose adjustments required for patients with hepatic dysfunction in the treatment or prophylaxis of influenza. (See section 5.2)

Elderly:

No dose adjustment is required for elderly patients in the treatment or prophylaxis of influenza.

Children:

The safety and efficacy of **MACSELTA 75 mg CAPSULES** in children under 1 year has not been established.

MACSELTA 75 mg CAPSULES should not be used in children under 1 year of age, other than during in a pandemic influenza outbreak.

***Method of administration*:**

Oral.

MACSELTA 75 mg CAPSULES may be taken with or without food. However, **MACSELTA 75 mg CAPSULES** taken with food may enhance tolerability in some patients.

Adults, adolescents or children who are unable to swallow capsules may receive appropriate doses of

MACSELTA 75 mg CAPSULES by opening capsules and pouring the contents of capsules 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 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 75 mg capsules: for patients requiring 30 – 60 mg doses, follow these instructions to ensure proper dosing: 1. Hold one **MACSELTA 75 mg CAPSULES** over a small bowl, carefully pull the capsule open and pour the powder into the bowl.

2. Add 5 mL water to the powder using a graduated syringe. Stir for approximately two minutes.

3. Draw up into the syringe the correct amount of mixture 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. Push down the plunger of the syringe to empty its entire contents into a second bowl. Discard any unused mixture.

Body Weight	**Recommended dose**	**Required amount of MACSELTA 75 mg CAPSULES mixture for one dose**
Less than or equal to 15 kg	30 mg	2 mL
More than 15 kg and up to 23 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, add a suitable, small amount (1 teaspoon maximum) of sweetened food product to the mixture (to mask the bitter taste) and mix well.

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

For patients requiring 75 mg dose, follow these instructions:

1. Hold one 75 mg capsule over a small bowl, carefully pull the capsule open and pour the powder

into the bowl.

2. Add a suitable, small amount (1 teaspoon maximum) of sweetened food product to the mixture (to mask the bitter taste) and mix well.

3. Stir the mixture and give the entire contents of the bowl to the patient. This mixture must be swallowed immediately after its preparation. If there is some mixture left inside the bowl, rinse the bowl with a small amount of water and have the patient drink this remaining mixture.

Repeat this procedure every time this medicine is taken.

4.3 Contraindications

Hypersensitivity to oseltamivir phosphate or to any component of **MACSELTA 75 mg CAPSULES** 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 **MACSELTA 75 mg CAPSULES** 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 **MACSELTA 75 mg CAPSULES**. Patients, and especially paediatric and adolescent patients, taking **MACSELTA 75 mg CAPSULES** should be carefully monitored.

There is no evidence for efficacy of **MACSELTA 75 mg CAPSULES** in any illness caused by agents other than influenza viruses types A and B. **MACSELTA 75 mg CAPSULES** is not a substitute for influenza vaccination.

Resistance of influenza viruses to **MACSELTA 75 mg CAPSULES** 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 **MACSELTA 75 mg CAPSULES**. The resistance of the predominant virus to **MACSELTA 75 mg CAPSULES** 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, **MACSELTA 75 mg CAPSULES** may only be used in infants 6-12 months of age for treatment during a pandemic influenza outbreak. The treating medical practitioner 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.

Dose adjustment is recommended for patients with creatinine clearance of 10 - 30 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 and section 5.2)

4.5 Interaction with other medicines and other forms of interaction

Information derived from pharmacology and pharmacokinetic studies of oseltamivir as contained in **MACSELTA 75 mg CAPSULES** suggest that clinically significant medicine interactions are unlikely. **MACSELTA 75 mg CAPSULES** 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. Low protein binding of **MACSELTA 75 mg CAPSULES** and the active metabolite do not suggest the probability of medicine displacement interactions. *In vitro* studies demonstrated that neither **MACSELTA 75 mg CAPSULES** nor the active metabolite is a good substrate for P450 mixed-function oxidases or for glucuronyl transferases.

There is no mechanistic basis for an interaction with oral contraceptives.

Cimetidine, a non-specific inhibitor of cytochrome P450 isoforms and competitor for renal tubular secretion of basic or cationic medicines has no effect on plasma levels of **MACSELTA 75 mg CAPSULES** or its active metabolite.

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. Co-administration of probenecid results in approximate 2-fold increase in exposure to the active metabolite due to a decrease in active tubular secretion in the kidney. However, due to the wide safety margin of the active metabolite, no dose adjustments are required when co-administering with probenecid.

Co-administration with amoxicillin does not alter plasma levels of either compound, indicating that competition for the anionic secretion pathway is weak.

Co-administration with paracetamol does not alter plasma levels of **MACSELTA 75 mg CAPSULES**, its active metabolite or paracetamol.

No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administrating **MACSELTA 75 mg CAPSULES** with paracetamol, acetyl-salicylic acid, cimetidine or with antacids (magnesium and aluminium hydroxides and calcium carbonates).

No change in adverse event profile or frequency has been observed as a result of co-administration of **MACSELTA 75 mg CAPSULES** with the following commonly used medicines:

ACE inhibitors (enalapril, captopril), thiazide diuretics (bendrofluazide), antibiotics (penicillin, cephalosporin, azithromycin, erythromycin and doxycycline), H_2-receptor blockers (ranitidine, cimetidine),beta-blockers(propranolol), xanthines (theophylline), sympathomimetics (pseudoephedrine), opioids (codeine), corticosteroids, inhaled bronchodilators and analgesic medicines (aspirin, ibuprofen and paracetamol). No change in adverse event profile or frequency has been observed as a result of co-administration of **MACSELTA 75 mg CAPSULES** with these compounds.

4.6 Fertility, pregnancy and lactation

Pregnancy

In animal reproductive studies in rats and rabbits, no teratogenic effect was observed. Fertility and reproductive toxicity studies have been conducted in rats. There was no evidence of an effect on fertility at any dose of **MACSELTA 75 mg CAPSULES** studied. Foetal exposure in rats and rabbits was approximately 15-20 % of that of the mother.

While no controlled clinical trials have been conducted on the use of **MACSELTA 75 mg CAPSULES** in pregnant women, there are limited data available from post-marketing and retrospective observational surveillance reports where pregnant women have used **MACSELTA 75 mg CAPSULES**; the data are insufficient to evaluate potential risk for **MACSELTA 75 mg CAPSULES** to cause foetal malformations or foetal toxicity, or to make a recommendation regarding its use during pregnancy.

Breastfeeding

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

Limited information is available on infants breastfed by mothers taking **MACSELTA 75 mg CAPSULES** and on excretion of **MACSELTA 75 mg CAPSULES** in breast milk. Limited data demonstrated that low levels of oseltamivir and the active metabolite were detected in breast milk. Mothers on treatment with **MACSELTA 75 mg CAPSULES** should not breastfeed their infants.

Fertility

Based on preclinical data, there is no evidence that **MACSELTA 75 mg CAPSULES** has an effect on male or female fertility.

4.7 Effects on ability to drive and use machines

MACSELTA 75 mg CAPSULES can cause side effects such as dizziness and visual disturbances, if these occur, your ability to drive or operate machinery may be impaired.

4.8 Undesirable effects

The following adverse reactions have been reported in association with **MACSELTA 75 mg CAPSULES**:

System Organ Class	**Frequency**	**Undesirable effects**
Infections and infestations:	Frequent	Bronchitis, herpes simplex, nasopharyngitis, upper respiratory tract infections, sinusitis, otitis media
Blood and lymphatic system disorders:	Less frequent	Thrombocytopenia, lymphadenopathy
Immune system disorders:	Less frequent	Anaphylactic reactions, anaphylactoid reactions, hypersensitivity reaction.
Psychiatric disorders:	Less frequent	Agitation, abnormal behaviour, anxiety, confusion, delusions, delirium, hallucination, nightmares, self-injury.

System Organ Class	Frequency	Undesirable effects
Nervous system disorders:	Frequent	Headache, insomnia, dizziness (including vertigo)
	Less frequent	Altered levels of consciousness, convulsion.
Eye disorders:	Less frequent	Visual disturbance, conjunctivitis (including red eyes, eye discharge and eye pain.
Ear and labyrinth disorders:	Frequent	Earache.
	Less frequent	Tympanic membrane disorder.
Cardiovascular disorders:	Less frequent	Cardiac dysrhythmia.
Respiratory, thoracic and mediastinal disorders:	Frequent	Cough, sore throat, rhinorrhoea, nasal congestion.
	Less frequent	Asthma (including aggravated), epistaxis.
Gastrointestinal disorders:	Frequent	Nausea, vomiting, abdominal pain (incl. upper abdominal pain), dyspepsia.
	Less frequent	Gastrointestinal bleedings, haemorrhagic colitis.
Hepatobiliary disorders:	Less frequent	Fulminant hepatitis, hepatic failure, hepatitis, elevated liver enzymes.
Skin and subcutaneous tissue disorders:	Less frequent	Angioneurotic oedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, eczema, dermatitis, rash, urticaria.
General disorders and administration site conditions:	Frequent	Pain, fatigue, pyrexia, pain in limb.

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 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

The anticipated manifestations of acute overdose would be nausea with or without accompanying emesis. No specific antidote is known.

5. PHARMACOLOGICAL PROPERTIES

Pharmaceutical classification: A 20.2.8 Antiviral agents

Pharmacotherapeutic group: Antivirals for systemic use neuraminidase inhibitors

ATC code: J05AH02

5.1 Pharmacodynamic properties

Oseltamivir phosphate is a pro-drug and selective inhibitor of influenza virus neuraminidase enzymes. Viral neuraminidase is essential for the release of recently formed virus particles from infected cells, and the further spread of infectious virus.

The active metabolite of oseltamivir inhibits neuraminidases of influenza viruses of both types A and B. The active metabolite also inhibits influenza virus growth *in vitro* and inhibits influenza virus replication and pathogenicity *in vivo*. The active metabolite reduces shedding of both influenza A and B virus by inhibiting the release of infectious virus from infected cells.

5.2 Pharmacokinetic properties

Absorption:

Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration of oseltamivir phosphate and is extensively converted predominantly by hepatic esterases to the active metabolite. Plasma concentrations of the active metabolite are measurable within 30 minutes, reach near maximal levels in 2 to 3 hours post dose, and substantially exceed (> 20-fold) those of the pro-drug. At least 75 % of an oral dose reaches the systemic circulation as the active metabolite.

Plasma concentrations of active metabolite are proportional to dose and are unaffected by co-administration with food.

Distribution:

The mean volume of distribution (V_{ss}) of the active metabolite is approximately 23 litres in humans. 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 drug 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.

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 (18,8l/h) exceeds glomerular filtration rate (7,5l/h) indicating that tubular secretion in addition to glomerular filtration occurs. Less than 20 % of an oral radio-labelled dose is eliminated in faeces.

Other special populations

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 30 mL/min. In patients with a creatinine clearance of 10 -30 mL/min, it is recommended that the dose be reduced to 75 mg of oseltamivir once daily for 5 days.

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 ≤10mL/min.

Prophylaxis of influenza: In patients with creatinine clearance between 10 and 30 mL/min receiving oseltamivir it is recommended that the dose be reduced to 75 mg of oseltamivir every other day or 30 mg suspension every day. 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 ≤10mL/min.

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. 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 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 for either the treatment or prophylaxis of influenza.

Children ≥1 year of age: The pharmacokinetics of oseltamivir has been evaluated in single dose pharmacokinetic studies in children aged 1to16 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 body weight, 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 range 3 to 16 years. Doses of 2 mg/kg yield oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75mg capsule dose (approximately 1mg/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 6-12 months provide exposures similar to those shown to be clinically efficacious in adults and children>1year of age.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity. Results of the conventional rodent carcinogenicity studies showed a trend towards a dose-dependent increase in the incidence of some tumours that are typical for the rodent strains used. Considering the margins of exposure in relation to the expected exposure in the human use, these findings do not change the benefit-risk of oseltamivir in its adopted therapeutic indications.

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

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

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

Whereas very high oral single doses of oseltamivir phosphate salt, up to the highest dose tested (1,310 mg/kg), had no adverse reactions in adult rats, such doses resulted in toxicity in juvenile 7-day-old rat pups, including death.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, povidone, pregelatinised starch, sodium stearyl fumarate, talc, hard gelatine capsules containing gelatine, iron oxide red, iron oxide yellow, iron oxide black and titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months from the manufacturing date

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Blister pack with silver coloured 25 micron aluminium foil / 6-8 gsm HSL as lidding material and clear film PVC/PE/PVdC: 250/25/60 micron as forming material containing 10 or 28 capsules. The blister shall be placed in a carton with package leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd

Office block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12,

Alberton, South Africa.

8. REGISTRATION NUMBER(S)

MACSELTA 75 MG CAPSULES: 52/20.2.8/0171

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 August 2021

10. DATE OF REVISION OF THE TEXT

31 March 2023

PM0053-01

Vanita Rajool

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