SCHEDULING STATUS S4

1 NAME OF THE MEDICINE
OSELFLU (Capsules)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
2ach capsule contains oseltamivir phosphate equivalent to 75 mg oseltamivir. For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
OSELFLU 75 mg gelatin capsule.
White to off white powder filled in size "2" hard gelatin capsule with cream cap and brown body printed OP on cap and 75 on body in black.

4 CLINICAL PARTICULARS
Therapeutic indications
OSELFLU is indicated in the following conditions:
- For the treatment and prophylaxis of influenza in adults and adolescents ≥ 13 years of age (see section 4.4).
- **OSELFLU** is not a substitute for influenza vaccination.

Posology and method of administration
Posology: OSELFLU may be taken with or without food (see section 5.2). However, **OSELFLU** taken with food may enhance tolerability in some patients.

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 of **OSELFLU** in adults and adolescents ≥ 13 years is a 75 mg capsule twice daily, for 5 days.
Children: Children > 40 kg or ≥ 8 years who are able to swallow capsules, may also receive treatment with a 75 mg capsule twice daily.
Prophylaxis of influenza:
The recommended oral dose of **OSELFLU** for prophylaxis of influenza following close contact with an infected individual is 75 mg once daily for at least 7 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. The duration of protection lasts for as long as dosing is continued.

Special Dosage Instructions:
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 **OSELFLU** 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 clearances 10 ml/min (see **Special populations** 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 **OSELFLU** it is recommended that the dose be reduced to 75 mg of **OSELFLU** 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 **Special populations** and section 4.4).
Patients with hepatic impairment
No dose adjustment is required for patients with hepatic dysfunction in the treatment or prophylaxis of influenza (see **Special populations** and section 4.4).
Elderly: No dose adjustment is required for elderly patients in the treatment or prophylaxis of influenza (see **Special populations** and section 4.4).
Children: The safety and efficacy of **OSELFLU** in children under 1 year has not been established (see **Special populations** and section 4.4).
OSELFLU should not be used in children under 1 year of age.

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 clearances ≤ 10 ml/min (see sections 4.2 and 4.4).
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. 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 sections 4.2 and 4.4).
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).
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 medicine exposure and tolerability, dosage adjustments are not required for elderly patients for either the treatment or prophylaxis of influenza (see section 4.2).
Paediatric population
The pharmacokinetics of oseltamivir have been evaluated in single dose pharmacokinetic studies in children aged 1 to 16 years. Younger children cleared both the pro-medicine and the active metabolite faster than adults resulting in 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 capsule dose (approximately 1 mg/kg). The pharmacokinetics of oseltamivir in children over 12 years of age are similar to those in adults.
Method of administration
Oral.

Contraindications
OSELFLU is contraindicated in the following conditions:
- Hypersensitivity to oseltamivir phosphate or to any component of **OSELFLU**.
- Pregnancy and lactation.
- Children under 1 year.

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 **OSELFLU** administration in patients with influenza. In rare cases, the delirium resulted in fatal accidental injury. These events occurred mostly within the first few days of taking **OSELFLU.** All patients taking **OSELFLU** should be carefully monitored for these adverse events. There is no evidence for efficacy of **OSELFLU** in any illness caused by agents other than influenza virus types A and B. **OSELFLU** is not a substitute for influenza vaccination. 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).

Paediatric population
The safety and efficacy of **OSELFLU** in children under 1 year has not been established (see section 4.3), therefore, **OSELFLU** should not be used in children under 1 year of age.
Interaction with other medicines and other forms of interaction
Information derived from pharmacology and pharmacokinetic studies of **OSELFLU** indicate that clinically significant medicine interactions are unlikely. 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 **OSELFLU** 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.
Additional information on special populations
Not applicable.
Paediatric population
Not applicable.

Fertility, pregnancy and lactation
Pregnancy
The safety and efficacy of **OSELFLU** during pregnancy have not been established (see section 4.3).
Breastfeeding
The safety and efficacy of **OSELFLU** during breastfeeding have not been established (see section 4.3).
Fertility
There is no evidence that **OSELFLU** has an effect on male or female fertility (see section 5.3).

Effects on ability to drive and use machines
OSELFLU can cause neuropsychiatric side effects that can influence a patient's ability to drive and use machines. Patients should be advised to not drive or use machines until they know how **OSELFLU** affects them (see section 4.8, Post-marketing experience).

Undesirable effects
a. Summary of the safety profile
Not applicable.

b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Frequency unknown	Lymphadenopathy
Nervous system disorders	Less Frequent	Headache, insomnia
Eye disorders	Less Frequent	Conjunctivitis
Ear and labyrinth disorders	Frequency unknown	Tympanic membrane disorder, otitis media
Respiratory, thoracic and mediastinal disorders	Less frequent	Bronchitis, epistaxis, cough
	Frequency unknown	Asthma (including aggravated), sinusitis, pneumonia
Gastrointestinal disorders	Frequent	Vomiting, nausea, diarrhoea
	Less frequent	Abdominal pain
Skin and subcutaneous tissue disorders	Frequency unknown	Dermatitis
General disorders and administration site conditions	Less frequent	Dizziness, fatigue

c. Description of selected adverse reactions
Not applicable
Post-marketing experience
Neuropsychiatric events such as convulsions, abnormal and inappropriate behaviour, disturbances in consciousness, hallucinations and delirium have been reported during **OSELFLU** administration in patients with influenza. In rare cases the delirium resulted in fatal accidental injury. These events occurred mostly within the first few days of taking **OSELFLU.** Patients, and especially paediatrics and adolescents, taking **OSELFLU** should be carefully monitored.
Skin and subcutaneous disorders
Rare cases of hypersensitivity reactions such as allergic skin reactions, including dermatitis, rash, eczema, urticaria, and very rare cases of erythema multiforme and Stevens-Johnson syndrome have been reported. Also, allergy, anaphylactic/anaphylactoid reactions and angioedema have been reported.
Liver and biliary system disorders
Very rare reports of hepatitis and elevated liver enzymes have been reported in patients with influenza-like illness receiving **OSELFLU.**
d. Paediatric population
Not applicable.
e. Other special population(s)
Not applicable.

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 The applicant can be reached at the following contact number: 010 045 2500.
Overdose
At present there has been no experience with overdose, however, the anticipated manifestations of acute overdose would be nausea, with or without accompanying emesis.
Additional information on special populations
Not applicable.
Paediatric population
Not applicable.

5 PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacological classification: A 20.2.8 Antivirals agents. Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors: ATC code: J05AH02.
Mechanism of action
Oseltamivir phosphate is a pro-medicine 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.
Paediatric population
Not applicable.

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-medicine. At least 75 % of an oral dose reaches the systemic circulation as the active metabolite. Plasma concentrations of the active metabolite are proportional to the dose and are unaffected by coadministration with food (see section 4.2).
Distribution
The mean volume of distribution (Vss) of the active metabolite is approximately 23 litres in humans. The active moiety reaches all key sites of influenza infections as shown by animal studies. The binding of the active metabolite to human plasma protein is negligible (approximately 3 %). The binding of the pro-medicine 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 metabolite 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 radiolabeled dose is eliminated in faeces.
Linearity/non-linearity
Not applicable.
Paediatric population
Not applicable.
Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity and genotoxicity.

6 PHARMACEUTICAL PARTICULARS
List of excipients
Granules: Croscarmellose sodium, Pregelatinized maize starch, Povidone, Sodium stearyl fumarate, Talc.
Hard gelatin capsule: Gelatin, Sodium laureth sulfate, Water, Iron oxide yellow, Iron oxide red, Titanium dioxide
Imprinting ink: Ammonia, Black iron oxide, Butyl alcohol, Dehydrated alcohol, Isopropyl alcohol, Potassium hydroxide, Propylene glycol, Shellac.
Incompatibilities
Not applicable.
Shelf life
4 Years. Store at or below 25°C.
Special precautions for storage
Protect from light. Keep blister in outer carton until required for use.
Nature and contents of container
Carton containing 10 capsules in blister pack. Blister packs are composed of plastic (PVC/PE/PVDC) and aluminiumfoil.
Special precautions for disposal and other handling
No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION
Strides Pharma SA (Pty) Ltd. 106 16th Road, Building 2, Midrand, 1686.

8 REGISTRATION NUMBER(S)
41/20.2.8/0798

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Renewal: April 2019

10 DATE OF REVISION OF THE TEXT
June 2020

Strides

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