SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

OSELTAMIVIR ADCO 30 mg, hard gelatine capsules

OSELTAMIVIR ADCO 45 mg, hard gelatine capsules

OSELTAMIVIR ADCO 75 mg, hard gelatine capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OSELTAMIVIR ADCO 30 mg: Each hard gelatine capsule contains oseltamivir phosphate equivalent to 30 mg oseltamivir.

OSELTAMIVIR ADCO 45 mg: Each hard gelatine capsule contains oseltamivir phosphate equivalent to 45 mg oseltamivir.

OSELTAMIVIR ADCO 75 mg: Each hard gelatine capsule contains oseltamivir phosphate equivalent to 75 mg oseltamivir.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatine capsules

OSELTAMIVIR ADCO 30 mg: Size “4” hard gelatine capsules with light yellow opaque body with black band, imprinted with “M” and light yellow opaque cap, imprinted with “30 mg”.

OSELTAMIVIR ADCO 45 mg: Size "4" hard gelatine capsules with grey opaque body with black band, imprinted with "M" and grey opaque cap, imprinted with "45 mg".

OSELTAMIVIR ADCO 75 mg: Size "2" hard gelatine capsules with grey opaque body with black band, imprinted with "M" and light yellow opaque cap, imprinted with "75 mg".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment

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

Prophylaxis

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

Pandemic use

OSELTAMIVIR ADCO 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 sections 4.4 and 5.2).

4.2 Posology and method of administration

Posology

OSELTAMIVIR ADCO may be taken with or without food (see section 5.2). However, **OSELTAMIVIR ADCO** 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 **OSELTAMIVIR ADCO 75 mg** capsules in adults and adolescents ≥ 13 years is a 75 mg capsule twice daily, for 5 days.

Adults and adolescents ≥ 13 years of age who are unable to swallow capsules may receive a dose of 75 mg oseltamivir 12 mg/mL oral suspension twice daily for 5 days.

Children

Children weighing > 40 kg or ≥ 8 years who are able to swallow capsules, may also receive treatment with a 75 mg capsule twice daily or one 30 mg capsule plus one 45 mg capsule twice a day as an alternative to the recommended dose of oseltamivir 12 mg/mL oral suspension (see below).

*The recommended weight-adjusted oral dose of **OSELTAMIVIR ADCO** for children ≥ 1 year of age is:*

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

*The recommended dose of **OSELTAMIVIR ADCO** 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.

The following dosing regimen is recommended for the treatment of children 6 – 12 months:

Body mass	***Recommended dose for 5 days***
6 kg	18 mg twice daily
7 kg	21 mg twice daily
8 kg	24 mg twice daily
9 kg	27 mg twice daily
≥ 10 kg	30 mg twice daily

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

The recommended treatment dose for infants 6 – 12 months is 3 mg/kg twice daily for 5 days, during a pandemic influenza outbreak only, and not for endemic (seasonal) influenza use (see section 5.2 – *Special patient populations)*.

Prophylaxis of influenza

Adults and adolescents

The recommended oral dose of **OSELTAMIVIR ADCO** for prophylaxis of influenza following close contact with an infected individual is 75 mg 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 75 mg once daily. Safety and efficacy have been demonstrated for up to 6 weeks.

The duration of protection lasts for as long as dosing is continued.

Children ≥ 1 year of age

Children with a body mass of > 40 kg, who are able to swallow capsules, may also receive prophylaxis with a 75 mg capsule once daily or one 30 mg capsule plus one 45 mg capsule once a day for 10 days as an alternative to the recommended dose of oseltamivir 12 mg/mL oral suspension.

*The recommended prophylactic oral dose of **OSELTAMIVIR ADCO** for children ≥ 1 year of age is:*

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

Special dosage instructions

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 **OSELTAMIVIR ADCO** 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 – *Special patient 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 a creatinine clearance between 10 and 30 mL/min receiving **OSELTAMIVIR ADCO** it is recommended that the dose be reduced to 75 mg of **OSELTAMIVIR ADCO** every other day or alternatively one 30 mg capsule 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 ≤ 10 mL/min. (see section 5.2 – *Special patient 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 section 5.2 – *Special patient populations*).

Elderly

No dose adjustment is required for elderly patients in the treatment or prophylaxis of influenza. (see section 5.2 – *Special patient populations*).

Children

The safety and efficacy of **OSELTAMIVIR ADCO** in children under 1 year has not been established (see *section 5.2 – Other special populations*). **OSELTAMIVIR ADCO** should not be used in children under 1 year of age, other than during a pandemic influenza outbreak.

Method of administration

Oral use.

Patients who are unable to swallow **OSELTAMIVIR ADCO** capsules may receive appropriate doses of oseltamivir oral suspension.

4.3 Contraindications

Hypersensitivity to oseltamivir phosphate or to any component of **OSELTAMIVIR ADCO** (see section 6.1).

4.4 Special warnings and precautions for use

Oseltamivir, as in **OSELTAMIVIR ADCO**, is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by medicines other than influenza viruses type A and B (see section 5.1).

OSELTAMIVIR ADCO *is not a substitute for influenza vaccination*.

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

Susceptibility of circulating influenza virus strains to oseltamivir has been shown to be highly variable (see section 5.1). Therefore, healthcare practitioners should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use **OSELTAMIVIR ADCO**.

Resistance of influenza viruses to oseltamivir, as in ***OSELTAMIVIR ADCO****, have been reported.* The prevalence of virus resistance and virus strains on subtypes differs between countries and seasons. In South Africa where H_1N_1 viruses predominated among circulating strains, 100 % [225/225] of H_1N_1 viruses tested in 2008 were resistant to oseltamivir. The resistance of the predominant virus to oseltamivir generally changes from season to season.

Severe concomitant condition

No information is available regarding the safety and efficacy of oseltamivir, as in **OSELTAMIVIR ADCO**, 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. However, the duration of treatment of influenza in immunocompromised adult patients should be 10 days, as there are no studies of a shorter course of oseltamivir in this patient group (see section 5.1).

Cardiac/respiratory disease

Efficacy of oseltamivir, as in **OSELTAMIVIR ADCO**, in the treatment of patients 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).

Paediatric population

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

Based on limited pharmacokinetic and safety data, **OSELTAMIVIR ADCO** may only be used in infants 6 – 12 months of age for treatment during a pandemic influenza outbreak. The treating physician 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 renal impairment

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 the end stage renal disease and for patients with creatinine clearance of ≤ 10 mL/min (see sections 4.2 and 5.2).

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 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 ≤ 10 mL/min (see sections 4.2 and 5.2)

Neuropsychiatric events

Neuropsychiatric events have been reported during administration of oseltamivir, as in **OSELTAMIVIR ADCO**, 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 (see section 4.8).

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 (see section 5.2), suggest that clinically significant medicine 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 medicine 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 ADCO** in patients taking co-excreted medicine with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate or phenylbutazone).

Additional information

No pharmacokinetic interactions between oseltamivir or its major metabolite have been observed when co-administering oseltamivir, as in **OSELTAMIVIR ADCO**, with paracetamol, acetylsalicylic acid, cimetidine, 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

Influenza is associated with adverse pregnancy and foetal outcomes, with a risk of major congenital malformations, including congenital heart defects. Post-marketing reports and observational studies indicate no malformative nor feto/neonatal toxicity by oseltamivir.

Animal studies do not indicate reproductive toxicity (see section 5.3). The use of **OSELTAMIVIR ADCO** 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 breastfed 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.

Mothers on treatment with **OSELTAMIVIR ADCO** should not breastfeed their infants.

Fertility

Based on preclinical data, there is no evidence that **OSELTAMIVIR ADCO** has an effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

It is not known whether **OSELTAMIVIR ADCO** could affect the ability to drive a vehicle or operate machinery.

However, if symptoms such as delirium or visual disturbance are experienced while taking **OSELTAMIVIR ADCO**, patients should be advised not to perform tasks requiring their attention.

4.8 Undesirable effects

In adults or adolescents, the frequently reported adverse reactions were nausea and vomiting. The majority of these adverse reactions were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1 – 2 days. In children, the frequenlty reported adverse reaction was vomiting. In the majority of patients, this side effect did not lead to discontinuation of oseltamivir.

The following serious adverse reactions have less frequently been reported:
Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders. (Regarding neuropsychiatric disorders, see section 4.4.)

Adverse reactions reported for the treatment and prevention of influenza in adults and adolescents or through post-marketing surveillance:

Infections and infestations

Frequent: bronchitis, bronchitis acute, herpes simplex, nasopharyngitis, upper respiratory tract infections, sinusitis

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, hallucinations, nightmares, self-injury

Nervous system disorders

Frequent: headache, insomnia

Less frequent: altered level of consciousness, convulsions

Eye disorders

Less frequent: visual disturbance

Cardiac disorders

Less frequent: cardiac dysrhythmia

Respiratory, thoracic and mediastinal disorders

Frequent: cough, sore throat, rhinorrhoea

Gastrointestinal disorders

Frequent: nausea, vomiting, abdominal pain (including upper abdominal pain), dyspepsia, diarrhoea

Less frequent: gastrointestinal bleedings, haemorrhagic colitis

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

General disorders and administration site conditions

Frequent: pain, dizziness (including vertigo), fatigue, pyrexia, pain in the limbs

Adverse reactions reported for the treatment and prevention of influenza in children (age/weight-based dosing [30 mg to 75 mg once daily])

Infections and infestations

Frequent: otitis media, bronchitis, pneumonia, sinusitis

Nervous system disorders

Frequent: headache

Eye disorders

Frequent: conjunctivitis (including red eyes, eye discharge and eye pain)

Ear and labyrinth disorders

Frequent: earache

Less frequent: tympanic membrane disorder

Respiratory, thoracic and mediastinal disorders

Frequent: cough, nasal congestion, rhinorrhoea, asthma (including aggravated)

Gastrointestinal disorders

Frequent: vomiting, abdominal pain (including upper abdominal pain, dyspepsia, nausea)

Skin and subcutaneous tissue disorders

Less frequent: dermatitis (including allergic and atopic dermatitis)

Disorders of the blood and lymphatic system

Less frequent: lymphadenopathy

Description of selected adverse reactions

Psychiatric disorders and nervous system disorders

Influenza can be associated with a variety of neurological 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.

Post marketing experience

Psychiatric disorder/Nervous system disorder

In patients with influenza who were receiving **OSELTAMIVIR ADCO**, 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 accidental self-injury and death. More events were reported in males than in females. The contribution of **OSELTAMIVIR ADCO** to those events is unknown. These neuropsychiatric events occurred mostly within the first few days of administration of **OSELTAMIVIR ADCO**. Patients, especially paediatric and adolescent

patients, should therefore be carefully monitored for the first few days. Convulsions and psychiatric symptoms have also been reported in patients with influenza who were not taking **OSELTAMIVIR ADCO**.

Skin and subcutaneous tissue disorder

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 are reported. Also, allergy, anaphylactic/anaphylactoid reactions and face oedema are reported rarely.

Hepato-biliary disorder

Very rare reports of hepatitis and elevated liver enzymes have been reported in patients with influenza-like illness receiving **OSELTAMIVIR ADCO**.

Gastrointestinal disorders

Gastrointestinal bleedings, in particular, haemorrhagic colitis were reported that subsided when the course of influenza abated or treatment with **OSELTAMIVIR ADCO** was interrupted.

Other special populations

Paediatric population (infants less than one year of age)

Safety information available on oseltamivir administered for treatment of influenza in infants less than one year of age from prospective and retrospective observational studies (comprising together more than 2 400 infants of that age class), 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

Treatment studies in 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) showed that the safety profile in the patients “at risk” was qualitatively similar to that in otherwise healthy adults/ adolescents.

Children with pre-existing bronchial asthma

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 **OSELTAMIVIR ADCO** is important. It allows continued monitoring of the benefit/risk balance of **OSELTAMIVIR ADCO**. Healthcare providers are asked to report any suspected adverse reactions via the **“6.04 Adverse Drug Reaction Reporting Form”**, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severety (see section 4.8).

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

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

Oseltamivir carboxylate inhibits influenza A and B neuraminidases *in vitro*. Oseltamivir phosphate inhibits influenza virus infection and replication *in vitro*. Oseltamivir inhibits influenza A and B virus replication and pathogenicity *in vivo.*

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 (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 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 is extensively converted to oseltamivir carboxylate by esterases located predominantly in the liver. *In vitr*o studies demonstrated that neither oseltamivir nor the active metabolite is a substrate for, or an inhibitor of, the major cytochrome P450 isoforms.

Elimination

Absorbed oseltamivir is primarily (> 90 %) eliminated by conversion to oseltamivir carboxylate. It is not further metabolised and is eliminated in the urine. Peak plasma concentrations of oseltamivir carboxylate decline with a half-life of 6 to 10 hours in most patients. The active metabolite is eliminated entirely by renal excretion. Renal clearance (18,8 L/h) exceeds glomerular filtration rate (7,5 L/h) indicating that tubular secretion occurs in addition to glomerular filtration. Less than 20 % of an oral radiolabelled dose is eliminated in faeces.

Special patient populations

Post-exposure prevention of influenza in infants less than 1 year of age during a pandemic

Simulation of once daily dosing of 3 mg/kg in infants < 1 year shows an exposure in the same range or higher than for once daily dosing of 75 mg in adults. Exposure does not exceed that for treatment of infants < 1 year (3 mg/kg twice daily) and is anticipated to result

in a comparable safety profile (see section 4.8). No clinical studies of prophylaxis in infants aged < 1 have been performed.

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.

Elderly patients

Exposure to the active metabolite at steady state was 25 to 35 % higher in older people (age 65 to 78 years) compared to adults less than 65 years of age given comparable doses of oseltamivir. Half-lives observed in older people were similar to those seen in young adults. On the basis of medicine exposure and tolerability, dosage adjustments are not required for older people unless there is evidence of moderate or severe renal impairment (creatinine clearance below 60 mL/min) (see section 4.2).

Renal impairment

Administration of 100 mg oseltamivir phosphate twice daily for 5 days to patients with various degrees of renal impairment showed that exposure to oseltamivir carboxylate is inversely proportional to declining renal function. For dosing, see section 4.2.

Hepatic impairment

In vitro studies have concluded that exposure to oseltamivir is not expected to be increased significantly nor is exposure to the active metabolite expected to be significantly decreased in patients with hepatic impairment (see section 4.2).

Pregnant women

A pooled population pharmacokinetic analysis indicates that the oseltamivir dosage regimen described in section 4.2 results in lower exposure (30 % on average across all trimesters) to the active metabolite in pregnant women compared to non-pregnant women. The lower predicted exposure however, remains above inhibitory concentrations (IC_{95} values) and at a therapeutic level for a range of influenza virus strains. In addition, there is evidence from observational studies showing benefit of the current dosing regimen in this patient population. Therefore, dose adjustments are not recommended for pregnant women in the treatment or prophylaxis of influenza (see section 4.6).

Immunocompromised patients

Population pharmacokinetic analysis indicates that treatment of adult immunocompromised patients with oseltamivir (as described in section 4.2) results in an increased exposure (of up to 50 %) to the active metabolite when compared to adult non-immunocompromised patients with comparable creatinine clearance. Due to the wide safety margin of the active metabolite, no dose adjustments are required in adults due to their immunocompromised status. However, for adult immunocompromised patients with renal impairment, doses should be adjusted as outlined in section 4.2.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule core:

Croscarmellose sodium

Povidone

Pregelatinised starch

Sodium stearyl fumarate

Talc

*Capsule shell for **OSELTAMIVIR ADCO 30 mg**:*

Gelatine

Iron oxide red (E172)

Iron oxide yellow (E172)

Titanium dioxide (E171)

*Capsule shell for **OSELTAMIVIR ADCO 45 mg**:*

Gelatine

Iron oxide black (E172)

Titanium dioxide (E171)

*Capsule shell for **OSELTAMIVIR ADCO 75 mg**:*

Gelatine

Iron oxide red (E172)

Iron oxide yellow (E172)

Iron oxide black (E172)

Titanium dioxide (E171)

Printing ink:

Ammonia solution (E527)

Iron oxide black (E172)

Potassium hydroxide (E525)

Propylene glycol (E1520)

Shellac (E904)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C.

Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

PVC/PE/PVdC aluminium blister pack containing 10 capsules.

One (1) or three (3) blister packs are packed in an outer carton.

Pack sizes: 10 or 30 capsules.

Not all pack sizes will be marketed.

6.6 Special precautions for disposal and other handling

When oseltamivir powder for oral suspension is not available

During situations when commercially manufactured oseltamivir powder for oral suspension is not readily available, adults, adolescents or children who are unable to swallow capsules

may receive appropriate doses of **OSELTAMIVIR ADCO** 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 mass*	**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

***** Children with a body mass > 40 kg may receive medication with the adult dosage of **OSELTAMIVIR ADCO 75 mg** capsules twice daily for 5 days for treatment and once daily for 10 days for prevention.

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 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.

When using the 75 mg capsules: for patients requiring 30 – 60 mg doses, follow these instructions to ensure proper dosing:

1. One **OSELTAMIVIR ADCO 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. 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 body mass of the patient. 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 mass	**Recommended dose**	**Required amount of OSELTAMIVIR ADCO 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 10 days for prevention.
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 mixed well.

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 mixed well.
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 OSELTAMIVIR ADCO is taken.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand, 1685

South Africa

Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBERS

OSELTAMIVIR ADCO 30 mg: 54/20.2.8/0687

OSELTAMIVIR ADCO 45 mg: 54/20.2.8/0688

OSELTAMIVIR ADCO 75 mg: 54/20.2.8/0689

9. DATE OF FIRST AUTHORISATION

03 November 2020

10. DATE OF REVISION OF THE TEXT

03 November 2020