PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

TAMYGEN Capsules

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each capsule contains oseltamivir phosphate equivalent to 75 mg oseltamivir base.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsules.

White to off-white powder filled in hard shell gelatin capsule with yellow opaque cap and white opaque body imprinted axially with ‘MYLAN’ over ‘OS3’ in black ink on cap and body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment: **TAMYGEN** is indicated for the treatment of influenza in adults and children ≥ 1 year of age (see sections 4.2 and 4.4).

Pandemic use: **TAMYGEN** 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).

Prophylaxis: **TAMYGEN** is indicated for the prophylaxis of influenza in adults and children ≥ 1 year of age.

4.2 Posology and method of administration

Posology

Treatment of influenza: Treatment should begin with the first or second day of onset of symptoms of influenza.

Adults and adolescents: The recommended oral dose of **TAMYGEN** in adults and adolescents ≥ 13 years is a 75 mg capsule twice daily, for 5 days.

Adults and adolescents ≥ 13 years of age that are unable to swallow capsules may receive an oral suspension (see “When Oral Suspension is not available”).

Children: Children > 40 kg or ≥ 8 years who are able to swallow capsules, may also receive treatment with a 75 mg capsule twice daily as an alternative to the oral suspension (see “When Oral Suspension is not available”).

The recommended oral dose of **TAMYGEN** for children 6-12 months of age: 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 the endemic (seasonal) influenza use.

Prophylaxis of influenza: The recommended oral dose of **TAMYGEN** 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 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 a 75 mg capsule 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 **TAMYGEN** 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 ≤ 10 mL/min (see sections 4.4 and 5.2).

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

TAMYGEN it is recommended that the dose be reduced to 75 mg of **TAMYGEN** 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 4.4 and 5.2).

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).

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 **TAMYGEN** in children younger than 1 year has not been established (see section 5.2). **TAMYGEN** should not be used in children under 1 year of age, other than during in a pandemic influenza outbreak.

When Oral Suspension is not available:

During situations when commercially manufactured oral suspension is not readily available: adults, adolescents or children who are unable to swallow capsules may receive appropriate doses of **TAMYGEN** 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 **TAMYGEN** capsule 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. (See table below for using 75 mg capsules).

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 this bowl, rinse the bowl with a small amount of water and have the patient drink this remaining mixture.

For patients requiring TAMYGEN 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.

Table for using 75 mg capsules:		
Body weight	Recommended dose	Required amount of **TAMYGEN** 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

Method of administration

Oral use.

TAMYGEN may be taken with or without food (see section 5.2). However, **TAMYGEN** taken with food may enhance tolerability in some patients.

4.3 Contraindications

- Known hypersensitivity to oseltamivir phosphate or to any of the excipients of **TAMYGEN** (see section 6.1).

4.4 Special warnings and precautions for use

Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses (see section 5.1).

TAMYGEN is not a substitute for influenza vaccination. Use of **TAMYGEN** must not affect the evaluation of individuals for annual influenza vaccination. The protection against influenza lasts only as long as **TAMYGEN** is administered. **TAMYGEN** 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, prescribers should take into account the most recent information available on oseltamivir susceptibility patterns of the currently circulating viruses when deciding whether to use **TAMYGEN**.

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. 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 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).

Paediatric population

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

Severe renal impairment

Dose adjustment is recommended for both treatment and prevention in adolescents (13 to 17 years of age) and adults with severe renal impairment. There is insufficient clinical data available in infants and children (1 year of age or older) with renal impairment to be able to make any dosing recommendation (see sections 4.2 and 5.2).

Neuropsychiatric events

Neuropsychiatric events such as convulsions, abnormal and inappropriate behaviour, disturbances in consciousness, hallucinations and delirium have been reported during administration of **TAMYGEN** in patients with influenza, especially in children and adolescents. These events are also experienced by patients with influenza without oseltamivir administration. Patients should be closely monitored for behavioural changes, and the benefits and risks of continuing treatment should be carefully evaluated for each patient (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 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 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 oseltamivir in subjects when taking co-excreted agents with a narrow therapeutic margin (e.g. chlorpropamide, methotrexate, phenylbutazone).

Additional information

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

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.

Foetal exposure in rats and rabbits was approximately 15 – 20% of that of the mother. While no controlled clinical trials have been conducted in pregnant women, there are limited data available from post-marketing and retrospective observational surveillance

reports where pregnant women have used oseltamivir; the data are insufficient to evaluate the potential risk for oseltamivir to cause foetal malformations or foetal toxicity, or to make a recommendation regarding its use during pregnancy.

Breast-feeding

In lactating rats, oseltamivir and the active metabolite are excreted in milk. Very limited information is available on children breast-fed by mothers taking oseltamivir and on excretion of oseltamivir in breast milk. Limited data demonstrated that oseltamivir and the active metabolite were detected in breast milk. Mothers on treatment with **TAMYGEN** should not breastfeed their infants.

Fertility

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

Animal studies do not indicate reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

TAMYGEN has a minor influence on the ability to drive and use machines. **TAMYGEN** may cause fatigue and dizziness (including vertigo) and patients should be advised to use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by **TAMYGEN** (see section 4.8).

4.8 Undesirable effects

a) Summary of adverse effects

The most frequently reported adverse reactions (ARs) were nausea and vomiting. The majority of these ARs were reported on a single occasion on either the first or second treatment day and resolved spontaneously within 1-2 days. In children, the most frequently reported adverse reaction was vomiting. In the majority of patients, these ARs did not lead to discontinuation of oseltamivir.

The following serious adverse reactions have been rarely reported since oseltamivir has been marketed: Anaphylactic and anaphylactoid reactions, hepatic disorders (fulminant hepatitis, hepatic function disorder and jaundice), angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis, gastrointestinal bleeding and neuropsychiatric disorders.

(Regarding neuropsychiatric disorders, see section 4.4.)

b) Tabulated summary of adverse reactions

Adverse reactions in studies investigating oseltamivir for treatment and prevention of influenza in adults ~~and~~ adolescents and children (age/weight-based dosing [30 mg to 75 mg once daily]) or through post-marketing surveillance:

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	Bronchitis, herpes simplex, nasopharyngitis, upper respiratory tract infections, sinusitis, otitis media
Blood and the 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, insomnia
	Less frequent	Altered level of consciousness, convulsion
Eye disorders	Frequent	Conjunctivitis (including red eyes, eye discharge and eye pain)
	Less frequent	Visual disturbance
Ear and labyrinth disorders	Frequent	Earache
	Less frequent	Tympanic membrane disorder
Cardiac disorders	Less frequent	Cardiac dysrhythmia
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, sore throat, rhinorrhea, nasal congestion and epistaxis
Gastrointestinal disorders:	Frequent	Nausea, vomiting, abdominal pain (incl. upper abdominal pain), dyspepsia

	Less frequent	Gastrointestinal bleedings, haemorrhagic colitis
Hepatobiliary disorders	Less frequent	Elevated liver enzymes, fulminant hepatitis, hepatic failure, hepatitis
Skin and subcutaneous tissue disorders:	Less frequent	Eczema, dermatitis (including allergic and atopic dermatitis), rash, urticaria, angioneurotic oedema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
General disorders and administration site conditions:	Frequent	Pain, dizziness (incl. vertigo), fatigue, pyrexia, pain in limb

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 oseltamivir, 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.

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.

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

At present there has been no experience with overdose however, the anticipated manifestations of acute overdose would be nausea, with or without accompanying emesis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, neuraminidase inhibitors ATC code: J05AH02

Pharmacological classification: A20.2.8 Antiviral agents

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 reduced 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 gastro-intestinal 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 interactions.

Metabolism

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 substance 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.

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 ≤ 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, as contained in **TAMYGEN**, it is recommended that the dose be reduced to 75 mg of **TAMYGEN** 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, as contained in **TAMYGEN**, 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 (range 65 – 78) compared to young adults who were given comparable doses of oseltamivir, as contained in **TAMYGEN**. Half-lives observed in the elderly were similar to those seen in young adults. On the basis of exposure and tolerability, dosage adjustments are not required for elderly patients for either the treatment or prophylaxis of influenza (see section 4.2).

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 range 3 to 16 years. Doses of 2 mg/kg yield oseltamivir carboxylate exposures comparable to those achieved in adults receiving a single 75 mg capsule (as in **TAMYGEN**) 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 sections 4.1 and 4.2).

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 Tamiflu 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.

These reactions were seen at doses of 657 mg/kg and higher. At 500 mg/kg, no adverse reactions were seen, including upon chronic treatment (500 mg/kg/day administered from 7 to 21 days post-partum).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill:

Croscarmellose sodium

Povidone

Pregelatinised starch

Sodium stearyl fumarate

Talc

Capsule shell:

Gelatin

Titanium dioxide (E171)

D&C yellow 10

FD&C yellow # 6

Imprinting ink:

Black iron oxide

Butyl alcohol

Dehydrated alcohol

Isopropyl alcohol

Potassium hydroxide propylene glycol

Shellac

Strong ammonia solution

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep blisters in outer carton until required for use.

Keep in the original container until required for use.

Do not use **TAMYGEN** after the expiry date shown on the box.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottle pack (30's and 100's) comprises of round wide mouth white High-Density Polyethylene bottle with white opaque polypropylene (PP) screw cap with induction sealing liner wad.

The HDPE bottle pack may be placed in an outer cardboard carton based on commercial requirement.

PVC/ PE / PVdC Blister pack (10's) comprises of clear transparent, PVC laminated with polyethylene which is further coated with PVDC. PVC blister pack (10's) comprises of clear transparent, non-toxic PVC film, sealed with aluminium foil.

Suitable number of blister strips will be placed in an outer cardboard carton. The number of capsules per strip and the number of strips in carton shall be based on commercial requirement.

6.6 Special precautions for disposal and other handling

No special precautions are required.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

MYLAN (PTY) LTD

4 Brewery Street

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Johannesburg, 1609

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8 REGISTRATION NUMBER

48/20.2.8/0963

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 July 2021

10 DATE OF REVISION OF TEXT