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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

OCUTRA CO eye drop solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OCUTRA CO: Each 1 ml of sterile solution contains 40 micrograms travoprost and timolol maleate equivalent to 5 mg timolol.

OCUTRA CO contains preservatives benzalkonium chloride 0,015 % m/v, boric acid 0,3 % m/v, edetate disodium 0,01 % m/v.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Eye drops, solution (eye drops).

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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Decrease of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma for whom treatment with either travoprost or timolol given alone provides insufficient IOP reduction.

4.2 Posology and method of administration

For ocular use.

Posology

Use in adults, including the elderly:

The dose is one drop of OCUTRA CO in the conjunctival sac of the affected eye(s) once daily, in the morning or evening. OCUTRA CO should be used at the same time each day.

Special populations

Use in hepatic and renal impairment:

No studies have been conducted with OCUTRA CO in patients with hepatic or renal impairment.

Travoprost, as in OCUTRA CO**,** has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dosage adjustment was necessary in these patients.

Paediatric population

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The efficacy and safety of OCUTRA CO in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.

Method of administration

The patient should remove the protective overwrap immediately prior to initial use. To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

Nasolacrimal occlusion or gently closing the eyelid after administration of OCUTRA CO is recommended. This may reduce the systemic absorption of OCUTRA CO administered via the ocular route and result in a decrease in systemic side effects.

If more than one topical ophthalmic medicine is being used, the medicines must be administered at least 5 minutes apart (see section 4.5).

When substituting another ophthalmic anti-glaucoma medicine with OCUTRA CO, discontinue the other medicine after proper dosing on one day and start the following day with OCUTRA CO.

4.3 Contraindications

K. Goolab

- hypersensitivity to travoprost, timolol or to any of the ingredients of OCUTRA CO
- bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease
- sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure or cardiogenic shock
- pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Children and adolescents under the age of 18 years:

The efficacy and safety of OCUTRA CO in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data becomes available.

Cardiac disorders:

Coronary heart disease, Prinzmetal's angina, cardiac failure and hypotension should be adequately controlled before beginning therapy with OCUTRA CO. Patients with cardiovascular diseases should be observed for signs of deterioration and have their pulse rates checked. Cardiac reactions and, in some cases, death in association with cardiac failure, have occurred following administration of OCUTRA CO.

Due to its negative effect on conduction time, OCUTRA CO should be given with caution

to patients with first degree heart block.

Respiratory disorders:

Respiratory reactions, including death due to bronchospasm in patients with asthma, have occurred following administration of OCUTRA CO (see section 4.3).

OCUTRA CO should be used with caution in patients with mild/moderate chronic obstructive pulmonary disease (COPD).

Vascular disorders:

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be given OCUTRA CO with caution.

Hypoglycaemia/diabetes:

OCUTRA CO should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) as timolol, as in OCUTRA CO, may mask the signs and symptoms of, and the response to, hypoglycaemia.

Anaphylactic reactions:

While taking OCUTRA CO, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual doses of

epinephrine (adrenaline) used to treat anaphylactic reactions.

Systemic effects:

OCUTRA CO is absorbed systemically. Timolol is a beta-blocker, therefore the same types of adverse reactions found with systemic administration of beta-blockers may occur with OCUTRA CO.

After topical ophthalmic administration, the incidence of systemic adverse reactions is lower than for systemic administration. For information on how to reduce systemic absorption, see section 4.2.

Muscle weakness:

OCUTRA CO can potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalised weakness).

Corneal diseases:

Ophthalmic timolol, as in OCUTRA CO, may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Choroidal detachment:

Choroidal detachment has been reported with administration of aqueous suppressant therapy, such as OCUTRA CO, after filtration procedures.

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Ocular effects:

Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatment with OCUTRA CO is commenced, patients must be informed of the possibility of a permanent change in eye colour. Unilateral
treatment can result in permanent heterochromia. The long term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. The change in eye colour has
predominantly been seen in patients with mixed coloured irides, i.e., blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. After discontinuation of therapy with OCUTRA CO, no further increase in brown iris pigment has been observed.

Periorbital and/or eyelid skin darkening in association with the use of OCUTRA CO has also been reported.

Periorbital and lid changes, including deepening of the eyelid sulcus, have been observed

K. Goolab

with prostaglandin analogues.

Travoprost may gradually change eyelashes in the treated eye(s); these changes include increased length, thickness, pigmentation, and/or number of lashes. The mechanism of eyelash changes and their long term consequences are unknown.

There is no experience of OCUTRA CO in inflammatory ocular conditions; nor in neovascular, angle-closure, narrow-angle or congenital glaucoma and only limited experience in thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma.

Caution is recommended when using OCUTRA CO in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema, as macular oedema has been reported during treatment with prostaglandin F2α analogues.

In patients with known predisposing risk factors for iritis/uveitis, OCUTRA CO can be used with caution.

Skin contact:

Travoprost, as in OCUTRA CO, is a biologically active substance that may be absorbed

through the skin. Women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of OCUTRA CO. In the unlikely event of coming into contact with a substantial portion of the contents of the OCUTRA CO bottle, thoroughly cleanse the
exposed area immediately.

Hyperthyroidism:

OCUTRA CO may also mask the signs of hyperthyroidism. Abrupt withdrawal of OCUTRA CO therapy may precipitate a worsening of symptoms.

Concomitant therapy:

OCUTRA CO may interact with other medicines. The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when OCUTRA CO is given to patients already receiving an oral beta-blocking medicine. The response of these patients should be closely observed. The use of two local beta-adrenergic blocking medicines or two local prostaglandins is not recommended.

Patients with phaeochromocytoma should not be given OCUTRA CO without alpha-adrenoceptor blocking therapy as well.

Surgery anaesthesia:

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OCUTRA CO may block systemic beta-agonist effects e.g. of epinephrine (adrenaline).

The anaesthesiologist should be informed when the patient is receiving OCUTRA CO.

Information on excipients of OCUTRA CO:

Benzalkonium chloride, used as a preservative in OCUTRA CO, may cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent or prolonged use of OCUTRA CO in dry eye patients, or in conditions where the cornea is compromised.

Benzalkonium chloride may cause irritation and is known to discolour soft contact lenses. Therefore, patients must remove contact lenses prior to application of OCUTRA CO and should be instructed to wait 15 minutes after instillation of OCUTRA CO before inserting contact lenses.

As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preservative cannot be excluded, regular ophthalmological examination is required. Caution

should be exercised in the use of OCUTRA CO over an extended period in patients with extensive ocular surface disease.

4.5 Interaction with other medicines and other forms of interaction

K. Goolab

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No specific interaction studies have been conducted with travoprost or timolol, as in OCUTRA CO.

There is a potential for additive effect results in hypotension and/or marked bradycardia when OCUTRA CO is administered concomitantly with oral calcium channel blockers, beta-blocking medicines, anti-dysrhythmics (including amiodarone), digoxin, guanethidine or parasympathomimetics.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when using timolol, as in OCUTRA CO.

Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has occurred during combined treatment with CYP2D6 inhibitors (e.g. quinidine, selective serotonin re-uptake inhibitors) and timolol contained in OCUTRA CO.

Mydriasis resulting from concomitant use of timolol, as in OCUTRA CO, and epinephrine (adrenaline) may occur.

Timolol, as in OCUTRA CO, may increase the hypoglycaemic effect of antidiabetic medicines. OCUTRA CO can mask the signs and symptoms of hypoglycaemia (see section 4.4).

K. Goolab

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4.6 Fertility, pregnancy and lactation

Women of childbearing potential

OCUTRA CO should not be used in women who may become pregnant unless adequate contraceptive measures are in place.

Pregnancy

There are no adequate data from the use of OCUTRA CO in pregnant women. Animal studies with travoprost, as in OCUTRA CO, have shown reproductive toxicity. OCUTRA CO should not be used during pregnancy (see section 4.3).

Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/newborn child.

Epidemiological studies have not revealed malformative effects but show a risk for intrauterine growth retardation when beta blockers are administered by the oral route. In addition, signs and symptoms of beta blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta blockers have been administered until delivery.

Breastfeeding

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Timolol, as in OCUTRA CO, is excreted in breast milk and has the potential to cause serious adverse reactions in the breast-fed infant. However, at therapeutic doses of timolol in eye drops it is unlikely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta blockade in the infant. For information on how to reduce systemic absorption, see section 4.2. Therefore, mothers breastfeeding their babies should not be treated with OCUTRA CO (see section 4.3).
It is unknown whether travoprost from eye drops is excreted in human breast milk, however, animal studies have shown excretion of travoprost and metabolites in breast milk.

Fertility

There are no data on the effects of OCUTRA CO on human fertility.

4.7 Effects on ability to drive and use machines

OCUTRA CO has minor influence on the ability to drive and use machines.
OCUTRA CO may cause temporary blurred vision or other visual disturbances which could affect the ability to drive and use machines. Patients should be advised to wait until their vision clears before driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

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Study data indicates the most frequently reported treatment-related adverse reaction is ocular hyperemia.

Tabulated list of adverse effects – OCUTRA CO

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	Frequency unknown	Agranulocytosis, increase in antinuclear antibodies, transient eosinophilia, non-thrombocytopenic purpura, thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity
Psychiatric disorders	Less frequent Frequency unknown	Nervousness Depression
Nervous system disorders	Less frequent Frequency unknown	Dizziness, headache Cerebrovascular accident, syncope, paraesthesia

K. Goolab

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Eye disorders	Frequent	Abnormal sensation in eye, dry eye, growth of eyelashes, ocular hyperaemia, eye irritation, punctate keratitis, eye pain, photophobia, eye pruritus,
	Less frequent	visual disturbance, blurred vision Eye allergy, anterior chamber cells, anterior chamber flare, asthenopia, blepharitis, allergic conjunctivitis, conjunctival haemorrhage, conjunctival oedema, distichiasis, eyelid margin crusting, dermatitis of eyelid, corneal erosion, erythema of eyelid, eyelid irritation, iritis, keratitis, increased lacrimation, meibomianitis, eyelid oedema, eyelid pain, periorbital disorder, ocular discomfort, photophobia, eyelids pruritus, corneal staining, eye swelling, trichiasis, reduced visual acuity, visual disturbance, xerophthalmia
	Frequency unknown	Corneal disorder, macular oedema, eyelid ptosis

K. Goolab

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Cardiac disorders	Less frequent Frequency unknown	Bradycardia, dysrhythmia, irregular heart rate Cardiac failure, chest pain, palpitations, tachycardia
Vascular disorders	Less frequent Frequency unknown	Hypertension, hypotension Peripheral oedema
Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Bronchospasm, cough, nasal discomfort, dysphonia, dyspnoea, postnasal drip, throat irritation, oropharyngeal pain Asthma
Gastrointestinal disorders	Frequency unknown	Dysgeusia
Hepatobiliary disorders	Less frequent	Increased alanine aminotransferase, increased aspartate aminotransferase
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Alopecia, contact dermatitis, skin discolouration, skin hyperpigmentation, hypertrichosis, urticaria Rash
Musculoskeletal, connective tissue and bone disorders	Less frequent	Pain in extremity

K. Goolab

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Renal and urinary disorders	Less frequent	Chromaturia
General disorders and administrative site conditions	Less frequent	Thirst, fatigue
Investigations	Less frequent Frequency unknown	Increased blood pressure, increased/decreased diastolic blood pressure, decreased heart rate, irregular heart rate, decreased intraocular pressure Changes in blood concentrations of triglycerides and cholesterol, raised liver enzymes

Additional adverse reactions that have been seen with one of the active substances and may potentially occur with OCUTRA CO. as individually indicated below.

Tabulated list of adverse effects – TRAVOPROST

System Organ Class	**Frequency**	**Side effects**
Immune system disorders	Frequency unknown	Seasonal allergy
Psychiatric disorders	Frequency unknown	Anxiety, insomnia
Nervous system disorders	Frequency unknown	Dizziness, headache

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Eye disorders	Frequency unknown	Conjunctival disorder, darkening, thickening and lengthening of eye lashes, darkening of palpebral skin, conjunctival follicles, conjunctival hyperaemia, transient punctuate, epithelial erosions, iris hyperpigmentation, severe iritis, ocular irritation, corneal, macular and eyelid oedema, uveitis, eye discharge, eyelids pruritus, ectropion, cataract, ophthalmic herpes simplex, photopsia, eczema eyelids, halo vision, hypoaesthesia eye, anterior chamber pigmentation, mydriasis, visual field defect
Ear and labyrinth disorders	Frequency unknown	Vertigo, tinnitus
Vascular disorders	Frequency unknown	Blood pressure diastolic decreased, blood pressure systolic increased
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Asthma aggravated, rhinitis allergic, epistaxis, respiratory disorder, nasal congestion, nasal dryness

K. Goolab

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Gastrointestinal disorders	Frequency unknown	Peptic ulcer reactivated, gastrointestinal disorder, diarrhoea, constipation, dry mouth, abdominal pain, nausea, vomiting
Skin and subcutaneous tissue disorders	Frequency unknown	Skin exfoliation, hair texture abnormal, dermatitis allergic, hair colour changes, madarosis, pruritus, hair growth abnormal, erythema
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Arthralgia, myalgia
Renal and urinary disorders	Frequency unknown	Dysuria, urinary incontinence
General disorders and administrative site conditions	Frequency unknown	Asthenia
Investigations	Frequency unknown	Prostatic specific antigen increased

Tabulated list of adverse effects – TIMOLOL

System Organ Class	**Frequency**	**Side effects**

K. Goolab

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Immune system disorders	Frequency unknown	Systemic allergic reactions including anaphylaxis, angioedema, pruritus, localised and generalised rash, systemic lupus erythematosus, urticaria
Metabolism and nutrition disorders	Frequency unknown	Hypoglycaemia, hyperglycaemia
Psychiatric disorders	Frequency unknown	Confusion, depression, hallucinations, insomnia, memory loss, nightmares
Nervous system disorders	Frequency unknown	Headache, cerebral ischaemia, dizziness, increase in signs and symptoms of myasthenia gravis
Eye disorders	Frequent Less frequent Frequency unknown	Choroidal detachment (following filtration surgery), conjunctivitis, decreased corneal sensitivity, diplopia, signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), decreased tear production, sore eyes, blurred vision diplopia

K. Goolab

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Cardiac disorders	Frequency unknown	Bradycardia, cardiac arrest, chest pains, congestive heart failure, heart block, palpitations, oedema, atrioventricular block
Vascular disorders	Frequency unknown	Hypotension, Raynaud's phenomenon, cold hands and feet
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Bronchospasm, dyspnoea, shortness of breath, pneumonitis, pulmonary fibrosis, pleurisy
Gastrointestinal disorders	Frequency unknown	Abdominal cramps and pain, constipation, diarrhoea, dry mouth, dysgeusia, dyspepsia, retroperitoneal fibrosis, nausea, sclerosing peritonitis, vomiting
Skin and subcutaneous tissue disorders	Frequency unknown	Reversible alopecia, pruritus, psoriasiform, rash or exacerbation of psoriasis, excess sweating
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Arthralgia and myopathies including muscle cramps, myalgia

K. Goolab

Reproductive system and breast disorders	Frequency unknown	Sexual dysfunction, decreased libido, male impotence
General disorders and administrative site conditions	Frequency unknown	Asthenia

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. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

In case of accidental ingestion with OCUTRA CO, symptoms may include hypotension, bradycardia, bronchospasm, heart failure, convulsions and coma.

Management of overdose:

If overdosage with OCUTRA CO occurs, treatment should be symptomatic and

supportive. Timolol, as in OCUTRA CO, does not dialyse readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; Antiglaucoma preparations and miotics

ATC code: S01ED51

Pharmacological classification: A.15.4 Ophthalmological preparations. Others

Mechanism of action

OCUTRA CO contains the two active substances travoprost and timolol. These two components lower intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone.

Travoprost:

Travoprost, a prostaglandin F2α analogue, is a full agonist which is highly selective and has a high affinity for the prostaglandin FP receptor, and reduces the intraocular pressure by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of IOP starts within approximately 2 hours after administration and maximum effect is reached after 12 hours. Significant lowering of intraocular pressure can be maintained for periods exceeding 24 hours with a single dose.

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Timolol maleate:

Timolol maleate is a non-selective adrenergic blocking medicine that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity.

Tonography and fluorophotometry studies suggest that its predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

5.2 Pharmacokinetic properties

Travoprost:

Absorption:

Travoprost is absorbed through the cornea. Travoprost is a prodrug that undergoes rapid ester hydrolysis in the cornea to the active free acid.

Following once-daily administration of 40 µg travoprost for 3 days, travoprost free acid was not quantifiable in plasma samples in the majority of patients (80 %) and was not detectable in any samples one hour after dosing.

Distribution:

Travoprost free acid can be measured in human plasma only during the first hour after ocular administration of travoprost.

Biotransformation:

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Metabolism is the major route of elimination of both travoprost and the active free acid. The systemic metabolic pathways parallel those of endogenous prostaglandin F2α which are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl and β-oxidative cleavages of the upper side chain.

Elimination:

Travoprost free acid and its metabolites are mainly excreted by the kidneys. Less than 2 % of an ocular dose of travoprost is recovered in urine as free acid.

Timolol maleate:

Absorption:

Timolol is absorbed through the cornea.

After once-daily administration of 5,0 mg timolol, mean steady-state C_{max} is 0,692 ng/ml and T_{max} approximately 1 hour.

Distribution:

After ocular administration of 5,0 mg, timolol can be measured in human aqueous humour and in plasma for up to 12 hours.

Biotransformation:

Timolol is metabolised by two pathways. One route yields an ethanolamine side chain on

K. Goolab

the thiadiazole ring and the other giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. After ocular administration of 5 mg timolol, the plasma t½ is 4 hours.

Excretion:

Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20 % of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium Chloride solution 50 % w/v

Boric Acid (preservative)

Edetate disodium (preservative)

Macrogolglycerol hydroxystearate

Mannitol

Sodium hydroxide 5N (for pH-adjustment)

Trometamol

K. Goolab

Water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze.

Keep vial tightly closed and in the carton when not in use.

Use within 28 days of opening.

6.5 Nature and contents of container

Transparent 5 ml polypropylene vial, sealed with a transparent LDPE dropper and white cap with a tamper-proof seal ring. The vial is enclosed in a white printed aluminium sachet (silver on the inside) and packed into an outer carton. Each vial is filled with 2,5 ml of solution.

6.6 Special precautions for disposal

No special requirements.

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7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, 7945

Cape Town

South Africa

8. REGISTRATION NUMBER(S)

A51/15.4/0099

9. DATE OF FIRST AUTHORISATION

14 April 2020

10. DATE OF REVISION OF THE TEXT

14 November 2024

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