PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

Latanoprost Unicorn, 50 micrograms/mL Eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL eye drop solution contains 50 micrograms of latanoprost.

One drop contains approximately 1,5 micrograms latanoprost.

Excipients with known effect

Benzalkonium chloride 0,02 % m/v is included as a preservative.

Sodium dihydrogen phosphate monohydrate 4,6 mg/mL.

Disodium phosphate anhydrous 4,74 mg/mL.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

A clear, colourless solution, free from visible particles of foreign matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of elevated intraocular pressure in patients with open angle glaucoma, chronic angle closure glaucoma and ocular hypertension.

In children less than 3 years of age, Latanoprost Unicorn can be initiated prior to other corrective procedures and may be continued if therapeutic response is adequate.

4.2 Posology and method of administration

Use in adults (including the elderly):

One drop in the affected eye(s) once daily. Optimal effect is obtained if Latanoprost Unicorn is administered in the evening.

The dosage of Latanoprost Unicorn should not exceed once daily since it has been shown that more frequent administration decreases the intra-ocular pressure lowering effect.

If one dose is missed, treatment should continue with the next dose as normal.

Reduction of the intraocular pressure starts about three to four hours after administration and maximum effect is reached after 8 to 12 hours. Pressure reduction is maintained for at least 24 hours.

Latanoprost Unicorn may be used concomitantly with other classes of topical ophthalmic medicines to lower intraocular pressure. If more than one topical ophthalmic medicine is being used, the medicines should be used at least five minutes apart.

Contact lenses should be removed before instillation of the eye drops and may be reinserted after fifteen minutes.

Special populations

Use in children:

Latanoprost Unicorn eye drops may be used in paediatric patients at the same posology as in adults. No data are available for preterm infants (less than 36 weeks gestational age). Data in the age group < 1 year are limited.

Method of administration

For opthalmic use.

4.3 Contraindications

Hypersensitivity to latanoprost, benzalkonium chloride or to any of the excipients listed in section 6.1.

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Latanoprost is hydrolysed in the cornea. The effect of constant administration of Latanoprost in the corneal epithelium has not been fully evaluated.

Iris pigmentation

Latanoprost Unicorn may gradually change eye colour by increasing the amount of brown pigment in the iris. Before treatment is initiated, patients should be informed of the likelihood of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia.

This change in eye colour has largely been seen in patients with mixed coloured irides, i.e. blue-brown, grey-brown, yellow-brown and green-brown. In studies with latanoprost, the commencement of the change is usually within the first 8 months of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. The rate of progression of iris pigmentation decreases with time and is stable for five years. The effect of increased pigmentation beyond five years has not been evaluated.

The colour change is owed to increased melanin content in the stromal melanocytes of the iris and not due to an increase in number of melanocytes. 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. No further increase in brown iris pigment has been observed after treatment is discontinued. The colour change has not been associated with any symptom or

pathological changes in clinical trials to date.

Neither naevi nor freckles of the iris have been affected by treatment. Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical trials. Based on 5 years of clinical experience, increased iris pigmentation has not been shown to have any negative clinical sequelae and Latanoprost Unicorn can be continued if iris pigmentation occurs. Intraocular pressure reduction was similar in patients regardless of the development of increased iris pigmentation. However, patients should be monitored regularly and if the clinical situation warrants, Latanoprost Unicorn treatment may be discontinued.

Glaucoma

There is limited experience of latanoprost in chronic angle closure glaucoma, open angle glaucoma of pseudophakic patients and in pigmentary glaucoma.

There is no experience of latanoprost in inflammatory and neovascular glaucoma or inflammatory ocular conditions. Latanoprost has no or little effect on the pupil, but there is no experience in acute attacks of closed angle glaucoma. There is limited experience with latanoprost in the treatment of congenital glaucoma. It is therefore recommended that Latanoprost Unicorn be used with caution in these conditions until more experience is obtained.

Cataract surgery

There are limited study data on the use of latanoprost during the peri-operative period of cataract surgery; therefore Latanoprost Unicorn should be used with caution in these patients.

Keratitis

Latanoprost Unicorn should be used with caution in patients with a history of herpetic keratitis, and should be avoided in cases of active herpes simplex keratitis

and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues.

Bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products has been reported. Patients must therefore be advised not to let the tip of the dispensing container contact the eye or surrounding structures as this could cause the tip to become contaminated by common bacteria known to cause ocular infections.

Macular oedema

The occurrence of macular oedema has been reported (see section 4.8) mainly in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema (such as diabetic retinopathy and retinal vein occlusion). Therefore, Latanoprost Unicorn should be used with caution in these patients.

Iritis/uveitis

Latanoprost Unicorn can be used with caution in patients with known predisposing risk factors for iritis/uveitis.

Asthma

There is limited experience from patients with asthma, but some cases of exacerbation of asthma and/or acute asthma attack, coughing, dyspnoea have been reported. Asthmatic patients should therefore be treated with caution until more experience is obtained, see also section 4.8.

Periorbital skin discolouration

Periorbital skin discolouration (eyelid skin darkening) has been reported. Experience

to date shows that periorbital skin discolouration is not permanent and in some cases has reversed whilst continuing treatment with latanoprost.

Eyelashes and vellus hair

Latanoprost Unicorn may gradually change eyelashes and vellus hair in the treated eye and surrounding areas; these changes include increased length, thickness, pigmentation, number of lashes or hairs and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.

Renal or hepatic impairment

The use of this medicine has not been studied in patients with renal or hepatic impairment and therefore Latanoprost Unicorn should be used with caution in such patients

Preservative

Latanoprost Unicorn contains benzalkonium chloride as a preservative.

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-preserved ophthalmological preparations cannot be excluded.

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface.

Therefore regular ophthalmological examination is necessary.

Caution should be exercised in dry eye patients and in patients where the cornea may be compromised, or patients with extensive ocular surface disease. Patients should be monitored in case of prolonged use.

From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger

reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children.

Contact lenses

Contact lenses may absorb benzalkonium chloride and the colour of the contact lenses may change. Patients should be advised to remove contact lenses before applying Latanoprost Unicorn and may reinsert them after 15 minutes (see section 4.2).

Paediatric population

Efficacy and safety data in the age group < 1 year are very limited. No data are available for preterm infants (less than 36 weeks gestational age).

In children from 0 to < 3 years old that mainly suffer from PCG (Primary Congenital Glaucoma), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment, as these children, prior to surgery for congenital glaucoma, respond poorly to latanoprost treatment.

Long-term safety in children has not yet been established.

4.5 Interaction with other medicines and other forms of interaction

Latanoprost is effective as monotherapy.

The effect of latanoprost in reducing intraocular pressure has been shown to be additive to that of ophthalmic beta-adrenergic antagonists (such as timolol).

In short term studies (up to 2 weeks) the effect of latanoprost was shown to be additive in combination with adrenergic agonists (dipivefrin), and oral carbonic anhydrase inhibitors (acetazolamide) and at least partly additive with cholinergic agonists (pilocarpine).

In conditions where combination therapy is necessitated, the eye drops should be administered with an interval of at least five minutes.

Definitive medicine interaction data are not available

There have been reports of inconsistent elevations in intraocular pressure following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended.

Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with eye drops containing latanoprost. If eye drops containing thiomersal are used with Latanoprost Unicorn these should be administered with an interval of at least five minutes.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of Latanoprost Unicorn in pregnancy is contraindicated (see section 4.3). It has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate. Therefore, Latanoprost Unicorn should not be used during pregnancy.

Breast-feeding

Latanoprost Unicorn is contraindicated in breastfeeding women (see section 4.3). Latanoprost and its metabolites may pass into breast milk and therefore Latanoprost Unicorn should not be used in breast-feeding women or breast feeding should be stopped.

Fertility

In animal studies Latanoprost was not found to have any effect on male or female fertility.

4.7 Effects on ability to drive and use machines

Latanoprost Unicorn has a minor influence on the ability to drive and use machines. Insertion of eye drops may cause temporary blurring of vision. Until this has resolved, patients should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The majority of adverse reactions relate to the ocular system. Patients developed iris pigmentation with use of latanoprost (see section 4.4). Other ocular adverse reactions are generally temporary and occur on dose administration.

Macular oedema including cystoid macular oedema has been reported during latanoprost treatment, mainly in patients with aphakia and pseudophakia with torn posterior lens capsule or anterior chamber lenses.

Systemic adverse events such as upper respiratory tract infection, colds and flu; pain in muscle, joints, back, chest pain and angina pectoris have been reported.

Tabulated list of adverse reactions

System Organ Class	Frequent	Less frequent	Frequency unknown
Infections and infestations			Herpetic keratitis
Nervous system disorders			Headache, dizziness
Eye disorders	Iris hyperpigmentation,	Eyelid oedema, dry Eye, trichiasis,	Eyelash and vellus hair changes of the

System Organ Class	Frequent	Less frequent	Frequency unknown
	mild to moderate conjunctival hyperaemia, eye irritation (burning grittiness, itching, stinging and foreign body sensation), punctate keratitis, mostly without symptoms, blepharitis, eye pain, photophobia	distichiasis, iris cyst, pseudopemphigoid of ocular conjunctiva, periorbital and lid changes resulting in deepening of the eyelid sulcus	eyelid (increased length, thickness, pigmentation and number of eyelashes), conjunctivitis, vision blurred, uveitis, iritis, keratitis, macular oedema including cystoid macular oedema, corneal erosion, misdirected eyelashes sometimes resulting in eye irritation, periorbital oedema, localised skin reaction on the eyelids, darkening of the palpebral skin of the eyelids
Cardiac disorders		Angina, angina unstable, aggravation of angina in patients with pre-existing disease	Palpitations
Respiratory, thoracic and mediastinal disorders			Asthma, dyspnea, asthma exacerbation, acute asthma attacks
Skin and subcutaneous tissue disorders		Rash, pruritus	

System Organ Class	Frequent	Less frequent	Frequency unknown
Musculoskeletal and connective tissue disorders			Myalgia, arthralgia
General disorders and administration site conditions			Chest pain

Less frequently cases of corneal calcification have been reported in association with the use of phosphate containing eye drops in some patients with considerably damaged corneas.

Paediatric population

Safety profile in paediatric patients is reported to be similar to that in adults. Most frequently reported adverse events in paediatric population as compared to adults are nasopharyngitis and pyrexia.

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.

Adverse reactions must also be reported to Unicorn Pharmaceuticals (Pty) Ltd to vigilance@unicornpharma.co.za

4.9 Overdose

Signs and Symptoms

In overdose, side effects will be exacerbated and exaggerated. Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if there is overdosage with Latanoprost Unicorn.

Management of overdose

If Latanoprost Unicorn is accidentally ingested the following information may be useful:

One 2,5 ml bottle contains 125 micrograms latanoprost. More than 90 % is metabolised during the first pass through the liver.

Intravenous infusion of 5,5 - 10 micrograms/kg in healthy volunteers caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating.

In patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically to the eyes in a dose of seven times the clinical dose of latanoprost.

If overdosage with Latanoprost Unicorn occurs, treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Category and class: A 15.4 Ophthalmic preparations: Others

Ophthalmologicals; Antiglaucoma preparations and miotics, prostaglandin analogues.

ATC code: S01EE01

Mechanism of action:

Latanoprost is a prostanoid selective prostaglandin F_2 (FP) receptor agonist, which reduces the intraocular pressure by increasing the outflow of aqueous humour.

Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow.

Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys.

Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term treatment.

5.2 Pharmacokinetic properties

Absorption

Latanoprost is absorbed through the cornea. Studies in man indicate that the peak concentration in the aqueous humour is reached about two hours after topical administration.

Distribution

The distribution volume in humans is 0,16 ± 0,02 L/kg. The acid of latanoprost can be measured in aqueous humour during the first four hours, and in plasma only during the first hour after local administration.

Metabolism

Latanoprost, an isopropyl ester prodrug, is hydrolysed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolised by the liver to the 1,2 dinor- and 1,2,3,4-tetranor-metabolites via fatty acid ß-oxidation.

Excretion

The elimination of the acid of latanoprost from human plasma is rapid (t½ = 17 minutes) after both intravenous and topical administration. Systemic clearance is approximately 7 ml/min/kg. Following hepatic ß-oxidation, the metabolites are

mainly eliminated via the kidneys. Approximately 88 % and 98 % of the administered dose is recovered in the urine after topical and intravenous dosing respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Benzalkonium chloride

Sodium dihydrogen phosphate monohydrate

Disodium phosphate anhydrous

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Before first opening: 2 years

After first opening of container: 4 weeks

6.4 Special precautions for storage

Store at 2 - 8 °C.

Once the container is opened it may be stored at or below 25 °C.

After first opening: Use within 4 weeks (see section 6.3).

Keep the bottle in the outer carton in order to protect from light.

Do not use the drops after the expiry date printed on the container.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6.5 Nature and contents of container

Latanoprost Unicorn is available in ethylene oxide sterilized polyethylene bottle with polyethylene nozzle and white polyethylene cap. Fill volume of 2.5 mL in 5 mL bottle.

Pack sizes: 2.5 mL

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Corner of Searle and Pontac Streets,

Woodstock, Cape Town, 8001

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8. REGISTRATION NUMBER(S)

52/15.4/0892

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 August 2022

10. DATE OF REVISION OF THE TEXT

Not applicable