SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Comarest, 50 microgram/ ml, Ophthalmic Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre contains latanoprost 50 microgram.

One drop contains approximately 1,5 microgram latanoprost.

Excipients with known effect:

Each millilitre contains benzalkonium chloride 0,02 % m/v as preservative.

Sodium dihydrogen phosphate monohydrate (E339i) 7,70 mg/ml.

Disodium phosphate anhydrous (E339ii) 1,55 mg/ml.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ophthalmic Solution

Sterile, colourless or pale yellow, clear solution.

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, Comarest can be initiated prior to other corrective procedures and may be continued if therapeutic response is adequate.

4.2 Posology and method of administration

Posology

Use in adults (including the elderly)

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

The dosage of Comarest 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. Comarest 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.

Use in children:

Comarest 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 ocular use only.

4.3 Contraindications

Known hypersensitivity to latanoprost, benzalkonium, or to any of the excipients of Comarest listed in 6.1.

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Ocular

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

The eye colour change is due to increased melanin content in the stromal melanocytes of the iris, rather than to an increase in number of melanocytes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. The change in iris colour is mild in the majority of cases and may not be detected clinically. The increase in iris pigmentation in one or both eyes has been documented predominantly in patients who have mixed coloured irides that contain the colour brown at baseline. Neither naevi nor freckles of the iris have been affected by treatment. No accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has been observed in clinical trials.

In a clinical trial designed to assess iris pigmentation over five years, there was no evidence of adverse consequences due to increased pigmentation even when administration of Comarest continued. In addition, IOP reduction was similar in patients regardless of the development of increased iris pigmentation. Therefore, treatment with Comarest can be continued in patients who develop increased iris pigmentation. These patients should be examined regularly and, depending on the clinical situation, treatment may be stopped.

Onset of increased iris pigmentation typically occurs within the first year 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 by five years. The effects of increased pigmentation beyond five years have not been evaluated. During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant colour change may be permanent.

Eyelid skin darkening, which may be reversible, has been reported in association with the use of Comarest.

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

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

Comarest 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.

Macular oedema, including cystoid macular oedema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular oedema (such as diabetic retinopathy and retinal vein occlusion). Caution is recommended when using Comarest in these patients.

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

There is limited experience from patients with asthma, but some cases of exacerbation of asthma and/or dyspnoea were reported in post marketing experience. Asthmatic patients should therefore be treated with caution until there is sufficient experience, see also section 4.8.

There is limited experience of Comarest in chronic angle closure glaucoma, open angle glaucoma of pseudophakic patients, angle closure congenital and in pigmentary glaucoma. There is no experience with Comarest in the treatment of inflammatory and neovascular glaucoma or inflammatory ocular conditions. Comarest has no or little effect on the pupil, but there is no experience in acute attacks of closed angle glaucoma.

Therefore, it is recommended that Comarest should, be used with caution in these conditions until more experience is obtained.

Comarest is hydrolysed in the cornea. The effect of continued administration of latanoprost in the corneal epithelium has not been fully evaluated.

Comarest has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. Patients must not let the tip of the dispensing container contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections.

Benzalkonium chloride:

Comarest contains benzalkonium chloride as a preservative. 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-preserved ophthalmological preparations cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride-preserved topical medication over an extended period in patients with extensive ocular surface disease, where the cornea may be compromised and in dry eye patients.

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

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. They should be removed before applying Comarest but may be reinserted 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 intraocular pressure reducing effect of latanoprost has been shown to be additive to that of beta-adrenergic antagonists (timolol).

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

In case of combined therapy, the eye drops should be administered with an interval of at least five minutes.

There have been reports of paradoxical elevations in IOP 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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

The use of Comarest in pregnancy and breastfeeding is contraindicated (see section 4.3).

Pregnancy

Latanoprost has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate, and should therefore not be used in pregnancy.

Breastfeeding

Latanoprost and its metabolites may pass into breast milk and Comarest should therefore not be used in breastfeeding women or breastfeeding should be stopped.

Fertility

Latanoprost has not been found to have any effect on male or female fertility in animal studies.

4.7 Effects on ability to drive and use machines

Instillation of eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Most undesirable effects observed relate to the ocular system. Latanoprost has caused increased pigmentation of the iris (see section 4.4). Macular oedema including cystoid macular oedema has been reported infrequently

during latanoprost treatment, mainly in patients with aphakia and pseudophakia with torn posterior lens capsule or anterior chamber lenses.

Systemic events:

The most common systemic adverse events seen with latanoprost were upper respiratory tract infection, colds and flu; pain in muscle, joints, back, chest pain and angina pectoris has also been reported.

Tabulated summary of adverse reactions

System Organ Classification	Frequency	Undesirable effects
Infections and infestations	*Less frequent*	Herpetic keratitis
Nervous system disorders	*Less frequent*	Headache; dizziness
Eye disorders	*Frequent*	Iris hyperpigmentation; mild to moderate conjunctival hyperaemia; eye irritation (burning grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation and number of eyelashes), punctate keratitis; mostly without symptoms; blepharitis; eye pain; photophobia; conjunctivitis
	Less frequent	Eyelid oedema; dry eye; keratitis; vision blurred; macular oedema including cystoid macular oedema; uveitis; iritis; corneal oedema; corneal erosion; periorbital oedema; trichiasis; distichiasis; iris cyst; localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids; pseudopemphigoid of ocular conjunctiva; periorbital and lid changes resulting in deepening of the eyelid sulcus
Cardiac disorders	*Less frequent*	Angina; palpitations; unstable angina, Aggravation of angina in patients with pre-existing disease
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Asthma; dyspnoea; asthma exacerbation
Skin and subcutaneous tissue disorders	*Less frequent*	Rash; pruritus
Musculoskeletal and connective tissue disorders	*Less frequent*	Myalgia; arthralgia
General disorders and administration site conditions	*Less frequent*	Chest pain

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eyedrops in some patients with significantly 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. Healthcare 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

In overdose, side effects will be exacerbated and exaggerated (see section 4.8). Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if Comarest is overdosed.

If Comarest 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.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 15.4 Ophthalmic preparations: Other

Pharmacotherapeutic group: Ophthalmologicals; Antiglaucoma preparations and miotics, prostaglandin analogues. ATC code: S 01 EE 01

Mechanism of action

Latanoprost is a prostanoid selective prostaglandin F2 (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 litre/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.

Biotransformation

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.

Elimination

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

Benzalkonium chloride

Disodium hydrogen phosphate anhydrous (E339ii)

Sodium chloride

Sodium dihydrogen phosphate monohydrate (E339i)

Water for injection

6.2 Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with Comarest. If such medicines are used, the eye drops should be administered with an interval of at least five minutes.

6.3 Shelf life

Before first opening: 2 years

Do not use more than 30 days after opening.

6.4 Special precautions for storage

Store in a refrigerator at 2 °C – 8 °C. Protect from light.

Once the container is opened the contents must be used within 30 days and may be stored at room temperature up to 25 °C. After opening, the container must be stored in the carton.

6.5 Nature and contents of container

It is supplied as a 3 ml solution in a 5 ml clear low density polyethylene (LDPE) bottle with a clear LDPE dropper tip and a high density polyethylene (HDPE) screw cap.

Each bottle contains 3 ml eye drop solution corresponding to approximately 80 drops.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Do not use more than 30 days after opening the container at 25 °C (see section 6.3).

7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8 REGISTRATION NUMBER

49/15.4/0154

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 July 2022

10 DATE OF REVISION OF THE TEXT

20 May 2022