SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Comarestol, 50 micrograms/ml + 5 mg/ml, Ophthalmic Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre contains 50 microgram latanoprost and 6,83 mg timolol maleate equivalent to 5 mg timolol.

Excipients with known effect:

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

Disodium phosphate, sodium dihydrogen phosphate monohydrate (containing total phosphate 6,3 mg/ml).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ophthalmic Solution

Sterile, colourless, clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who are not controlled on, or are intolerant to, monotherapy with compounds other than latanoprost and timolol.

4.2 Posology and method of administration

Posology

The tamper evident overcap should be removed before use.

Use in adults (including the elderly)

One drop in the affected eye(s) once daily.

The dosage of Comarestol 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 planned.

Paediatric population:

Safety and effectiveness in children have not been established.

Method of administration

For ocular use only.

If more than one topical ophthalmic medicine is being used, they should be administered at least 5 minutes apart.

4.3 Contraindications

Known hypersensitivity to latanoprost, timolol maleate, benzalkonium, or to any of the excipients of Comarestol listed in 6.1.

Reactive airway disease including bronchial asthma or a history of bronchial asthma, chronic obstructive pulmonary disease.

Sinus bradycardia, second or third degree atrioventricular block, cardiac failure, cardiogenic shock.

Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Systemic effects

Comarestol is absorbed systemically. Due to the beta-adrenergic component timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-adrenergic blocking medicines may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

Cardiac disorders

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Aggravation of Prinzmetal’s angina, hypotension, bradycardia, cardiac reactions, and rarely, death in association with cardiac failures have been reported following administration of timolol.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution, as aggravation of peripheral and central circulatory disorders may occur after topical application of timolol maleate as in Comarestol.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. Comarestol should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycaemia/diabetes

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may increase the hypoglycaemic effect of medicines used to treat diabetes and may mask the signs and symptoms of acute hypoglycaemia.

Beta-blockers may also mask the signs of hyperthyroidism. Abrupt withdrawal of therapy may precipitate a worsening of this condition.

Corneal diseases

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Other beta-blocking medicines

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking medicine. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking medicines is not recommended (see section 4.5).

Anaphylactic reactions

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

A gradual withdrawal of beta-adrenergic blocking medicines prior to major surgery should be considered. Beta-adrenergic blocking medicines impair the ability of the heart to respond to beta-adrenergically mediated reflex stimuli, which may augment the risk of general anaesthesia in surgical procedures.

Protracted severe hypotension during anaesthesia and difficulty restarting and maintaining the heartbeat have been reported. During surgery, the effects of beta-adrenergic blocking medicines may be reversed by sufficient doses of adrenergic agonists.

Concomitant therapy

Timolol may interact with other medicines see section 4.5. The concomitant use of Comarestol with hypoglycaemic medicines, phenothiazines and various antidysrhythmic medicines may have interactions with life-threatening consequences.

Other prostaglandin analogues

The concomitant use of two or more prostaglandins, prostaglandin analogues, or prostaglandin derivatives is not recommended (see section 4.5).

Timolol maleate has been reported to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms (e.g. diplopia, ptosis, generalised weakness).

Iris pigmentation changes

Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Similar to experience with latanoprost eye drops, increased iris pigmentation was seen in patients treated with latanoprost-timolol for up to one year. This effect has predominantly been seen in patients with mixed coloured irides that contain the colour brown at baseline, i.e. green-brown, yellow-brown or blue/grey-brown, and is due to increased melanin content in the stromal melanocytes of the iris, rather than to an increase in the 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. In patients with homogeneously blue, grey, green or brown eyes, the change has only rarely been seen during two years of treatment in clinical trials with latanoprost.

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.

The change in iris colour occurs slowly and may not be noticeable for several months to years and it has not been associated with any symptom or pathological changes.

No further increase in brown iris pigment has been observed after discontinuation of treatment, but the resultant colour change may be permanent.

IOP reduction was similar in patients regardless of the development of increased iris pigmentation. Therefore, treatment with latanoprost 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.

Neither naevi nor freckles of the iris have been affected by the treatment.

Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed but patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased iris pigmentation ensues.

Before treatment is instituted patients should be informed of the possibility of a change in eye colour. Unilateral treatment can result in permanent heterochromia.

Eyelid and eyelash changes

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

Latanoprost may gradually change eyelashes and vellus hair in the treated eye; 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.

Glaucoma

There is no documented experience with latanoprost in inflammatory, neovascular, or chronic angle closure glaucoma, in open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. Latanoprost has no or little effect on the pupil but there is no documented experience in acute attacks of closed angle glaucoma. Therefore, it is recommended that Comarestol should be used with caution in these conditions until more experience is obtained.

Herpetic keratitis

Latanoprost 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

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 a torn posterior lens capsule, or in patients with known risk factors for macular oedema. Comarestol should be used with caution in these patients.

Benzalkonium chloride:

Comarestol contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctuate keratopathy and/or toxic ulcerative keratopathy, may cause eye irritation. Close monitoring with regular ophthalmological examination is required with frequent or prolonged use of Comarestol in dry eye patients, or in conditions where the cornea is compromised due to extensive ocular surface disease.

Contact lenses

Contact lenses may absorb benzalkonium chloride, which is known to discolour soft contact lenses and these should be removed before applying Comarestol but may be reinserted after 15 minutes (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

No specific medicine interaction studies have been performed with Comarestol.

There have been reports of paradoxical 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.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking medicines, anti-dysrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

Potentiated systemic beta blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when Comarestol is given to patients already receiving an oral beta-adrenergic blocking medicine, and the use of two or more topical beta-adrenergic blocking medicines is not recommended.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

Beta-blockers may increase the hypoglycaemic effect of anti-diabetic medicines. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).

The concomitant use of Comarestol with hypoglycaemic medicines, phenothiazines and various anti-dysrhythmic medicines may have interactions with life-threatening consequences.

4.6 Fertility, pregnancy and lactation

Pregnancy

Comarestol is contraindicated in pregnancy (see section 4.3).

Breastfeeding

Comarestol should not be used in breastfeeding women, or breastfeeding should be stopped as timolol is excreted into breast milk and latanoprost and its metabolites may pass into breast milk (see section 4.3).

Fertility

Neither Latanoprost nor timolol have 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

The adverse events of Comarestol are similar to those reported earlier for latanoprost and timolol (see section 4.4). Based on evidence from consecutive photographs, increased iris pigmentation was seen in 16 – 20 % of all patients who received latanoprost-timolol eye drops for up to one year.

The most frequent findings of increased iris pigmentation were in patients with green-brown, yellow-brown and blue/grey/brown irides. In patients with homogenously blue, grey, green or brown eyes, the change was only rarely seen.

Darkening, thickening and lengthening of the eye lashes has been reported.

The most frequently reported undesirable effects in clinical trials were irritation of the eye, including stinging, burning and itching, eye hyperaemia, corneal disorders, conjunctivitis, blepharitis, eye pain, headache and skin rash.

Table 1: Adverse reactions associated with Latanoprost-Timolol preparations

System Organ Classification	Frequency	Undesirable effects
Infections and infestations	*Frequent*	Infection, sinusitis, upper respiratory tract infection
Metabolism and nutrition disorders	*Frequent*	Diabetes mellitus, hypercholesterolaemia
Psychiatric disorders	*Frequent*	Depression
Nervous system disorders	*Frequent*	Headache
Eye disorders	*Frequent*	Eye irritation (including stinging, burning, itching, foreign body sensation), eye pain, increased iris pigmentation, abnormal vision, cataract, conjunctival disorder, keratitis, photophobia, visual field defect, errors of refraction
	Less frequent	Corneal disorders, conjunctivitis, blepharitis, eye hyperaemia, increased lacrimation
Vascular disorders	*Frequent*	Hypertension
Skin and subcutaneous tissue disorders	*Frequent*	Hypertrichosis, rash, skin disorder
	Less frequent	Pruritus
Musculoskeletal and connective tissue disorders	*Frequent*	Arthritis

Table 2: Adverse reactions associated with Latanoprost

System Organ Classification	Frequency	Undesirable effects
Infections and infestations	*Frequency unknown*	Herpetic keratitis
Nervous system disorders	*Frequency unknown*	Dizziness
Eye disorders	*Frequent*	Eye irritation (burning, grittiness, itching, stinging and foreign body sensation), eyelid oedema, punctate keratitis
	Frequency unknown	Eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes); misdirected eyelashes sometimes resulting in eye irritation, periorbital oedema; iritis; uveitis; macular oedema including cystoid macular oedema dry eye; keratitis; corneal oedema; corneal erosion; trichiasis; iris cyst; photophobia; periorbital and lid changes resulting in deepening of the eyelid sulcus; eyelid oedema; localised skin reaction on the eyelids;

System Organ Classification	Frequency	Undesirable effects
		pseudopemphigoid of the ocular conjunctiva[+]; darkening of the palpebral skin
Cardiac disorders	*Frequency unknown*	Angina; angina unstable; palpitations
Respiratory, thoracic and mediastinal disorders	*Frequency unknown*	Asthma; asthma aggravation; dyspnoea, acute asthma attacks
Skin and subcutaneous tissue disorders	*Frequent*	Skin rash
Musculoskeletal and connective tissue disorders	*Frequency unknown*	Myalgia; arthralgia
General disorders and administration site conditions	*Frequency unknown*	Non-specific chest pain

[+] May be potentially related to the preservative benzalkonium chloride

Table 3: Timolol Maleate (ocular administration)

System Organ Classification	Frequency	Undesirable effects
Immune system disorders	*Frequency unknown*	Systemic allergic reactions including anaphylactic reaction, angioedema, urticaria, localised and generalised rash, pruritus
Metabolism and nutrition disorders	*Frequency unknown*	Anorexia, masked symptoms of hypoglycaemia in diabetic patients
Psychiatric disorders	*Frequency unknown*	Behavioural changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss, decreased libido, insomnia, nightmares, depression
Nervous system disorders	*Frequency unknown*	Cerebrovascular accident, cerebral ischaemia, dizziness, increases in signs and symptoms of myasthenia gravis, paraesthesia, headache, syncope
Eye disorders	*Frequency unknown*	Choroidal detachment following filtration surgery (see section 4.4), corneal erosion, keratitis, diplopia, decreased corneal sensitivity, signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing and redness), dry eyes, ptosis, blepharitis, blurred vision
Ear and labyrinth disorders	*Frequency unknown*	Tinnitus
Cardiac disorders	*Frequency unknown*	Cardiac arrest, atrioventricular block, congestive heart failure, chest pain, dysrhythmia, bradycardia, oedema, palpitations, worsening of angina pectoris
Vascular disorders	*Frequency unknown*	Cold hands and feet, hypotension, Raynaud's phenomenon, claudication
Respiratory, thoracic and mediastinal disorders	*Frequency unknown*	Bronchospasm (predominately in patients with pre-existing bronchospastic disease), cough, dyspnoea, nasal congestion, pulmonary oedema, respiratory failure
Gastrointestinal disorders	*Frequency unknown*	Abdominal pain, vomiting, diarrhoea, dry mouth, dysgeusia, dyspepsia, nausea, retroperitoneal fibrosis
Skin and subcutaneous tissue disorders	*Frequency unknown*	Skin rash, psoriasiform rash, exacerbation of psoriasis, alopecia
Musculoskeletal and connective tissue disorders	*Frequency unknown*	Myalgia, Systemic lupus erythematosus
Reproductive system and breast disorders	*Frequency unknown*	Sexual dysfunction, decreased libido, Peyronie's disease

System Organ Classification	Frequency	Undesirable effects
General disorders and administration site conditions	*Frequency unknown*	Asthenia, fatigue, chest pain, oedema

Cases of corneal calcification have been reported less frequent in association with the use of phosphate containing eyedrops in some patients with significantly damaged corneas.

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

No data are available in humans with regard to overdose with Comarestol.

Symptoms

Symptoms of systemic timolol overdose are: bradycardia, hypotension, bronchospasm and cardiac arrest.

Apart from ocular irritation and conjunctival hyperaemia, no other ocular or systemic side effects are known if latanoprost is overdosed. In patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost such as contained in Comarestol when applied topically in the eyes in a dose seven times the clinical dose of latanoprost.

There have been reports of inadvertent overdosage with latanoprost-timolol eye drops resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking medicines such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest.

Treatment

If symptoms of overdose occur the treatment should be symptomatic and supportive.

If accidentally ingested orally the following information may be useful:

Studies have shown that timolol does not dialyse readily. Latanoprost is extensively metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers induced no symptoms, but a dose of 5,5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. These events were mild to moderate in severity and resolved without treatment, within 4 hours after terminating the infusion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 15.4 Ophthalmic preparations: Other

Pharmacotherapeutic group: Ophthalmological-betablocking agents - timolol, combinations

ATC code: S01ED51

Mechanism of action

Comarestol consists of two components: latanoprost and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by different mechanisms of action.

Latanoprost, a prostaglandin F2α analogue, is a prostanoid selective prostaglandin F2 (FP) receptor agonist that reduces the IOP by increasing the outflow of aqueous humour.

The main mechanism of action is increased uveoscleral outflow. Additionally, some increase in outflow activity (decrease in trabecular outflow resistance) has been reported in man.

Latanoprost has no significant effect on the production of aqueous humour, the blood-aqueous barrier or the intraocular blood circulation. Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term treatment.

Timolol is a beta-1 and beta-2 (non-selective) adrenergic receptor blocking medicine. Timolol lowers IOP by decreasing aqueous humour formation in the ciliary epithelium. The precise mechanism of action has not been clearly established.

Pharmacodynamic effects:

Clinical effects:

Onset of action of Comarestol is within one hour, and maximal effect occurs within six to eight hours. IOP reducing effect has been shown to be present up to 24 hours post dosage after multiple treatments.

5.2 Pharmacokinetic properties

Latanoprost

Absorption

Latanoprost is an isopropyl ester prodrug, which per se is inactive but after hydrolysis by esterases in the cornea to the acid of latanoprost, becomes biologically active. The prodrug is well absorbed through the cornea and all drug that enters the aqueous humour is hydrolysed during the passage through the cornea.

Distribution

Studies in man indicate that the maximum concentration in the aqueous humour, approximately 30 ng/mL, is reached about 2 hours after topical administration of latanoprost alone. After topical application in monkeys latanoprost is distributed primarily in the anterior segment, the conjunctiva and the eye lids.

The acid of latanoprost has a plasma clearance of 0,40 l/h/kg and a small volume of distribution, 0,16 l/kg, resulting in a rapid half-life in plasma, 17 minutes. After topical ocular administration the systemic bioavailability of the acid of latanoprost is 45 %. The acid of latanoprost has a plasma protein binding of 87 %.

Biotransformation and elimination

There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. The main metabolites, the 1,2-dinor and 1,2,3,4-tetranor metabolites, exert no or only weak biological activity in animal studies and are excreted primarily in the urine.

Timolol

Absorption and distribution

The maximum concentration of timolol in the aqueous humour is reached about 1 hour after topical administration of eyedrops. Part of the dose is absorbed systemically and a maximum plasma concentration of 1 ng/mL is reached 10-20 minutes after topical administration of one eye drop to each eye once daily (300 micrograms/day).

Biotransformation

The half-life of timolol in plasma is about 6 hours. Timolol is extensively metabolised in the liver.

Elimination

The metabolites are excreted in the urine together with some unchanged timolol.

Comarestol

Pharmacokinetic/pharmacodynamic relationship

No pharmacokinetic interactions between latanoprost and timolol were observed, although there was an approximate 2-fold increased concentration of the acid of latanoprost in aqueous humour 1-4 hours after administration of Comarestol compared to monotherapy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Disodium hydrogen phosphate anhydrous

Sodium chloride

Sodium dihydrogen phosphate monohydrate

Water for injection

6.2 Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with Comarestol. 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: 3 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 to protect it from light.

6.5 Nature and contents of container

Comarestol is packaged in a multi-dose low density polyethylene (LDPE) bottle of 5 ml nominal volume with a clear LDPE dropper and high density polyethylene (HDPE) screw cap. The bottle is labelled and is supplied in a conventional boxboard carton with a patient information leaflet (PIL).

Each bottle contains 2,5 ml eye drop solution.

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

49/15.4/0155

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 August 2022

10 DATE OF REVISION OF THE TEXT

12 April 2022