SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

XALACOM® 50 micrograms/mL + 5 mg/mL, eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains latanoprost 50 micrograms and timolol maleate equivalent to 5 mg timolol.

Preservative: Benzalkonium chloride 0,02 % m/v.

One drop contains approximately 1,5 micrograms latanoprost and 150 micrograms timolol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution

A clear and colourless solution, free of visible particles.

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

Use in adults (including the elderly)

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

The dosage of XALACOM should not exceed once daily since it has been shown that more frequent administration of latanoprost decreases the intraocular pressure lowering effect.

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

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

minutes apart.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced.

Paediatric population

Safety and effectiveness in children have not been established.

Method of administration

For ophthalmic use.

The tamper evident overcap should be removed before use.

4.3 Contraindications

- Known hypersensitivity to latanoprost, timolol maleate or to any of the excipients of XALACOM (listed in section 6.1).
- Bronchial asthma or a history of bronchial asthma, chronic obstructive pulmonary disease (COPD).
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second- or third-degree atrioventricular block not controlled with pacemaker, cardiac failure or cardiogenic shock.
- Active herpes simplex keratitis or recurrent herpetic keratitis specifically associated with prostaglandin analogues (see section 4.4).

4.4 Special warnings and precautions for use

Latanoprost

Iris pigmentation changes

Latanoprost may gradually increase the brown pigment of the iris. The eye colour change 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 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 colour irides that contain the colour brown at baseline. Neither nevi 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 latanoprost continued. These results are consistent with post-marketing clinical experience since 1996. In addition, 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.

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 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.

The potential for heterochromia exists for patients receiving unilateral treatment.

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 torn posterior lens capsule, or in patients with known risk factors for macular oedema. Caution is recommended when using XALACOM in these patients.

Glaucoma

There is no documented experience with latanoprost-timolol in inflammatory, neovascular, chronic angle closure or congenital glaucoma, in open-angle glaucoma of pseudophakic patients and in pigmentary glaucoma. Therefore, it is recommended that XALACOM 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 is contraindicated in cases of active herpes simplex keratitis and in patients with a history of recurrent herpetic keratitis specifically associated with prostaglandin analogues (see section 4.3).

Timolol

Systemic effects

The same adverse reactions found with systemic administration of beta-adrenergic blocking medicines may occur with their topical administration. Patients with a history of severe cardiac disease should be monitored closely for signs of cardiac failure. The following cardiac and respiratory reactions may occur after topical application of timolol maleate as in XALACOM:

- Aggravation of Prinzmetal's angina.
- Aggravation of peripheral and central circulatory disorders.
- Hypotension.
- Cardiac failure resulting in death.
- Severe respiratory reactions, including fatal bronchospasm in patients with asthma.
- Bradycardia.

Cardiac disorders

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

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.

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

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.

Surgical anaesthesia

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

Hypoglycaemia/diabetes

Beta-adrenergic blocking medicines may increase the hypoglycaemic effect of medicines used to treat diabetes and mask the signs and symptoms of hypoglycaemia. They should be used with caution in patients with spontaneous hypoglycaemia or diabetes (especially those with labile diabetes), who are receiving insulin or oral hypoglycaemic medicines.

Therapy with beta-adrenergic blocking medicines may mask certain signs and symptoms of hyperthyroidism. Abrupt withdrawal of therapy may precipitate a worsening of this condition.

Anaphylactic reactions

When treated with beta-adrenergic blocking medicines, patients with a history of atopy or severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens. They may be unresponsive to the usual doses of epinephrine (adrenaline) used to treat anaphylactic reactions.

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

Choroidal detachment

Choroidal detachment after filtration procedures has been reported with the administration of ocular hypotensive medicines.

Corneal diseases

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

Benzalkonium chloride

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised.

Patients should be monitored in case of prolonged use.

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 medicine over an extended period in patients with extensive ocular surface disease.

Use of contact lenses

XALACOM contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, may cause eye irritation and is known to discolour soft contact lenses. Close monitoring is required with frequent or prolonged use of XALACOM in dry eye patients, or in conditions where the cornea is compromised. Contact lenses may absorb benzalkonium chloride and these should be removed before applying XALACOM but may be reinserted after 15 minutes.

Timolol may interact with other medicines, see section 4.5.

4.5 Interaction with other medicines and other forms of interaction

Specific interaction studies have not been performed with XALACOM.

The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when XALACOM 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.

There have been reports of paradoxical elevations in intraocular pressure (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.

The potential exists for additive effects resulting in hypotension and/or marked bradycardia when eye drops containing timolol are administered with calcium-channel blockers, catecholamine-depleting medicines or beta-blocking medicines, anti-dysrhythmics (including amiodarone and quinidine), digitalis glycosides, parasympathomimetics, narcotics and monoamine oxidase (MAO) inhibitors.

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.

Although XALACOM alone has little or no effect on pupil size, mydriasis has occasionally been reported when timolol is given with epinephrine (adrenaline).

Beta-blockers may increase the hypoglycaemic effect of anti-diabetic medicines (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety in pregnancy has not been established.

Breastfeeding

XALACOM should not be used in women who are breastfeeding their infants. Breastfeeding should be stopped as timolol is excreted into breast milk and latanoprost and its metabolites may pass into breast milk.

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 XALACOM are similar to those reported for latanoprost and timolol.

For latanoprost, the majority of adverse reactions relate to the ocular system. In data from the extension phase of the XALACOM pivotal trials, 16 – 20 % of developed increased iris pigmentation, which may be permanent.

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.

Tabulated summary of adverse reactions

The tables below contain side effects categorised as follows utilising the incidence rates: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

Latanoprost-timolol (clinical trials)		
MedDRA System organ class	**Frequency**	**Undesirable effects**
Infections and infestations	Common	Infection, sinusitis, upper respiratory tract infection
Metabolism and nutrition disorders	Common	Diabetes mellitus, hypercholesterolaemia
Psychiatric disorders	Common	Depression
Nervous system disorders	Common	Headache
Eye disorders	Very common	Eye irritation, increased iris pigmentation
	Common	Abnormal vision, blepharitis, cataract, conjunctival disorder, conjunctivitis, corneal disorder, errors of refraction, eye hyperaemia, eye pain, keratitis, photophobia, visual field defect
Vascular disorders	Common	Hypertension
Skin and subcutaneous tissue disorders	Common	Hypertrichosis, rash, skin disorder
Musculoskeletal and connective tissue disorders	Common	Arthritis

Latanoprost (clinical trials)		
MedDRA System organ class	**Frequency**	**Undesirable effects**
Eye disorders	Very common	Eye irritation (burning, grittiness, itching, stinging and foreign body sensation)
	Common	Eyelid oedema, transient punctate epithelial erosions
Skin and subcutaneous tissue disorders	Common	Skin rash

Latanoprost post-marketing surveillance	
MedDRA System organ class	**Undesirable effects**
Infections and infestations	Herpetic keratitis
Nervous system disorders	Dizziness
Eye disorders	Eyelash and vellus hair changes (increased length, thickness, pigmentation, and number), blurred vision, iritis/uveitis, macular oedema including cystoid macular oedema, corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation, photophobia, periorbital and lid changes resulting in deepening of the eyelid sulcus
Respiratory, thoracic and mediastinal disorders	Asthma, dyspnoea, asthma aggravation, acute asthma attacks
Skin and subcutaneous tissue disorders	Localised skin reaction on eyelids, darkening of palpebral skin of the eyelids
Musculoskeletal and connective tissue disorders	Muscle/joint pain
General disorders and administration site conditions	Non-specific chest pain

Timolol maleate (ocular administration)	
MedDRA System organ class	**Undesirable effects**
Immune system disorders	Signs and symptoms of systemic allergic reactions including

	anaphylaxis, angioedema, urticaria, pruritus, localised and generalised rash
Metabolism and nutrition disorders	Anorexia, masked symptoms of hypoglycaemia in diabetic patients
Psychiatric disorders	Behavioural changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss, decreased libido, insomnia, depression, nightmares
Nervous system disorders	Dizziness, paraesthesia, somnolence, headache, cerebral ischaemia, cerebral vascular accident, increase in signs and symptoms of myasthenia gravis, syncope
Eye disorders	Visual disturbance including refractive changes and diplopia, ptosis, cystoid macular oedema, decreased corneal sensitivity, signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), blepharitis, keratitis, blurred vision, dry eyes, corneal erosion, choroidal detachment following filtration surgery
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Dysrhythmia, bradycardia, atrioventricular block, congestive heart failure, palpitation, cardiac arrest, cardiac failure, heart block, worsening of angina pectoris
Vascular disorders	Claudication, hypotension, cold hands and feet, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, bronchospasm (predominately in patients with pre-existing bronchospastic disease), nasal congestion, pulmonary oedema, respiratory failure
Gastrointestinal disorders	Diarrhoea, dry mouth, dysgeusia, dyspepsia, nausea, vomiting, abdominal pain, retroperitoneal fibrosis
Skin and subcutaneous tissue	Alopecia, pseudopemphigoid, skin rash, psoriasiform rash or

disorders	exacerbation of psoriasis
Musculoskeletal and connective tissue disorders	Systemic lupus erythematosus, myalgia
Reproductive system and breast disorders	Decreased libido, impotence, sexual dysfunction, Peyronie's disease
General disorders and administration site conditions	Asthenia/fatigue, chest pain, oedema

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

Apart from ocular irritation and conjunctival hyperaemia, no other ocular or systemic side effects are known if latanoprost is overdosed. Symptoms of systemic timolol overdosage are bradycardia, hypotension, bronchospasm and cardiac arrest. If such symptoms occur, the treatment should be symptomatic and supportive.

If latanoprost is accidentally ingested, the following 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 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. In patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost such as included in XALACOM when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost. Studies have shown that timolol does not dialyse readily.

There have been reports of inadvertent overdosage with XALACOM 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Ophthalmologicals – Beta blocking agents – timolol, combinations

ATC code: S01ED51

Category and class: A 15.4 Ophthalmic preparations: Others

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

Latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a prostanoid selective prostaglandin F_2 (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.

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.

Onset of action of XALACOM 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

Latanoprost is an isopropyl ester prodrug that 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 medicine that enters the aqueous humour is hydrolysed during the passage through the cornea. The maximum concentration in the aqueous humour, approximately 30 ng/mL, is reached about 2 hours

after topical administration of latanoprost alone.

The acid of latanoprost has a plasma clearance of 0,4 L/h/kg and a small volume of distribution, 0,16 L/kg, resulting in a rapid half-life in plasma of 17 minutes.

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 and are excreted primarily in the urine.

Timolol

The maximum concentration of timolol in the aqueous humour is reached about one hour after topical administration of eye drops. 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). The half-life of timolol in plasma is about 4 hours. Timolol is extensively metabolised in the liver. The metabolites are excreted in the urine together with some unchanged timolol.

XALACOM

No pharmacokinetic interactions between latanoprost and timolol were observed, although there is a tendency for increased concentrations of the acid of latanoprost in aqueous humour 1 to 4 hours after administration of XALACOM compared to monotherapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Disodium phosphate anhydrous

Sodium chloride

Sodium dihydrogen phosphate monohydrate

Water for injections

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

- Store in a refrigerator between 2 °C – 8 °C in the original carton.
- Once the bottle is opened the contents must be used within 30 days and may be stored at room temperature at or below 25 °C.
- After opening, the bottle must be stored in the carton to protect it from light.

6.5 Nature and contents container

The drops are available in a 5 mL multidose, clear, colourless, low-density polyethylene bottle, with a clear, linear, low- or medium-density polyethylene dropper tip (applicator), protected with a yellow inner high-density polyethylene screw cap, and a clear, colourless tamper-evident overcap of low-density polyethylene.

Each bottle contains 2,5 mL eye drop solution.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel.: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

Manufacturer: Pfizer Manufacturing Belgium NV, Puurs, Belgium

8. REGISTRATION NUMBER

36/15.4/0043

9. DATE OF FIRST AUTHORISATION

15 November 2002

10. DATE OF REVISION OF THE TEXT

20 April 2022

NAMIBIA: NS2

Reg. No.: 08/15.4/0146

ZIMBABWE: PP10

Reg. No.: 2010/19.10/4604