SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

XALATAN® EYE DROPS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains latanoprost 50 µg.

One drop contains approximately 1,5 µg latanoprost.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

The solution is a clear, colourless liquid.

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, XALATAN 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 XALATAN is administered in the evening.

The dosage of XALATAN 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.

XALATAN 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.

Paediatric population

XALATAN 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 (4 patients) are limited (see section 5.1).

Method of administration

For ophthalmic use.

4.3 Contraindications

- Known hypersensitivity to latanoprost, benzalkonium chloride or to any of the excipients of XALATAN (listed in section 6.1).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Ocular

XALATAN 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 number of melanocytes. Typically, 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 XALATAN continued. Intraocular pressure (IOP) reduction was similar in patients regardless of the development of increased iris pigmentation. Therefore, treatment with XALATAN 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 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 XALATAN.

XALATAN 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, including cystoid macular oedema, has been reported during treatment with XALATAN. 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 XALATAN in these patients.

There is limited experience with XALATAN in the treatment of inflammatory neovascular, angle closure congenital or pigmentary glaucoma and also in pseudophakic patients with open angle glaucoma. Therefore, it is recommended that XALATAN should be used with caution in these conditions until more experience is obtained.

XALATAN 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 XALATAN should be used with caution in these conditions until more experience is obtained.

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

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

XALATAN 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.

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.

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

Asthma

There is limited experience in patients with asthma, but cases of asthma, asthma aggravation, acute asthma attack, coughing and dyspnoea have been reported.

Benzalkonium chloride

XALATAN contains benzalkonium chloride, which may be absorbed by contact lenses.

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

Paediatric population

Efficacy and safety data in the age group < 1 year (4 patients) are very limited (see section 5.1). 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 XALATAN treatment.

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

4.5 Interaction with other medicines and other forms of interaction

XALATAN is effective as monotherapy.

The intraocular pressure-reducing effect of XALATAN has been shown to be additive to that of beta-adrenergic antagonists (timolol).

In short-term studies (up to 2 weeks) the effect of XALATAN 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, 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

Pregnancy

The use of XALATAN in pregnancy is contraindicated. XALATAN 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 (see section 4.3).

Breastfeeding

The safety in lactation has not been established. Mothers treated with XALATAN should not breastfeed their infants (see section 4.3).

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.

XALATAN has caused increased pigmentation of the iris (see section 4.4).

Macular oedema including cystoid macular oedema has been reported during XALATAN 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 XALATAN were:

- Upper respiratory tract infections.
- Colds and flu.
- Pain in muscles, joints, back pain.
- Chest pain and angina pectoris has also been reported.

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).

Clinical trials

MedDRA system organ class	**Frequency**	**Side effects**
Eye disorders	Very common	Iris hyperpigmentation, eye irritation (burning, grittiness, itching, stinging and foreign body sensation)
	Common	Blepharitis, eye pain, eyelid oedema, mild to moderate conjunctival hyperaemia, punctate keratitis mostly without symptoms
Cardiac disorders	Uncommon	Angina
Skin and subcutaneous tissue disorders	Common	Rash
	Rare	Pruritus

Post-marketing surveillance

MedDRA system organ class	Side effects
Infections and infestations	Herpetic keratitis
Nervous system disorders	Dizziness, headache
Eye disorders	Eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eye lashes), conjunctivitis, blurred vision, iritis, uveitis, keratitis, macular oedema including cystoid macular oedema, corneal oedema, corneal erosion, trichiasis, periorbital oedema, photophobia, periorbital and lid changes resulting in deepening of the eyelid sulcus, localised skin reaction on eyelids, darkening of palpebral skin of the eyelids, iris cyst, pseudopemphigoid of ocular conjunctiva
Cardiac disorders	Palpitations, unstable angina
Respiratory, thoracic and mediastinal disorders	Asthma, dyspnoea, asthma aggravation, acute asthma attacks
Gastrointestinal disorders	Nausea, vomiting
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia
General disorders and administration site conditions	Chest pain

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Paediatric population

In two short-term clinical trials (≤ 12 weeks) involving 93 (25 and 68) paediatric patients, the safety profile was similar to that in adults and no new adverse events were identified. The short-term safety profiles in the different paediatric subsets were also similar (see section 5.1). Adverse events seen more frequently in the 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.

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 XALATAN is overdosed.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 15.4 Ophthalmic preparations: Others

Mechanism of action

Latanoprost is a prostanoid selective prostaglandin F_2 (FP) receptor agonist, which reduces the IOP 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.

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.

Paediatric population

An open-label pharmacokinetic study of plasma latanoprost acid concentrations was undertaken in 22 adults and 25 paediatric patients (from birth to < 18 years of age) with ocular hypertension and glaucoma. All age groups were treated with latanoprost 0,005 %, one drop daily in each eye for a minimum of 2 weeks. Latanoprost acid systemic exposure was approximately 2-fold higher in 3 to < 12-year-olds and 6-fold higher in children < 3 years old compared with adults, but a wide safety margin for systemic adverse effects was maintained (see section 4.9). Median time to reach peak plasma concentration was 5 minutes post-dose across all age groups. The median plasma elimination half-life was short (< 20 minutes), similar for paediatric and adult patients, and resulted in no accumulation of latanoprost acid in the systemic circulation under steady-state conditions.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Disodium phosphate anhydrous

Sodium chloride

Sodium dihydrogen phosphate monohydrate

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

36 months.

6.4 Special precautions for storage

- Store in a refrigerator between 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 at or below 25 °C. **After opening, the container must be stored in the carton.**

6.5 Nature and contents of container

The drops are available in a 5 mL colourless, transparent polyethylene bottle, with a dropper applicator, protected with an inner screw cap, and a tamper-evident overcap of polyethylene.

Each bottle contains 2,5 mL eye drop solution corresponding to approximately 80 drops.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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Manufacturer: Pfizer Manufacturing Belgium NV, Puurs, Belgium.

8. REGISTRATION NUMBER

31/15.4/0614

9. DATE OF FIRST AUTHORISATION

25 September 1997

10. DATE OF REVISION OF THE TEXT

22 November 2022

NAMIBIA: NS2

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