SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

XALATAN® EYE DROPS

COMPOSITION:

Each millilitre contains latanoprost 50 µg and benzalkonium chloride 0,02 % m/v as preservative.

One drop contains approximately 1,5 µg latanoprost.

PHARMACOLOGICAL CLASSIFICATION:

A 15.4 Ophthalmic preparations: Others

PHARMACOLOGICAL ACTION:

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.

Pharmacokinetics:

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 ($t_{½}$ = 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.

INDICATIONS:

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

CONTRAINDICATIONS:

Known hypersensitivity to latanoprost, benzalkonium chloride or any other component in XALATAN.

WARNINGS:

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, 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 XALATAN 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 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 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 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 or congenital glaucoma. Therefore, it is recommended that XALATAN should, be used with caution in these conditions until more experience is obtained.

Benzalkonium chloride:

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.

INTERACTIONS:

Pivotal studies demonstrated that XALATAN 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 analogs. Therefore, the use of two or more prostaglandins, prostaglandin analogs, or prostaglandin derivatives is not recommended.

Incompatibilities:

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

PREGNANCY AND LACTATION:

Pregnancy:

The safety of XALATAN for use in pregnancy has not been established. 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.

Lactation:

The safety in lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

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 in man 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.

Use in children:

Safety and effectiveness in children have not been established.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Most undesirable effects observed relate to the ocular system.

XALATAN has caused increased pigmentation of the iris – see WARNINGS.

Macular oedema including cystoid macular oedema has been reported infrequently 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 infection, colds and flu; pain in muscle, joints, back, chest pain and angina pectoris has also been reported.

The tables below contain side effects categorised as follows utilising the incidence rates: Very common ≥ 1/10 (≥ 10 %); Common ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %); Uncommon ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %); Rare ≥ 1/10 000 and < 1/1 000 (≥ 0,01 % and < 0,1 %); Very rare < 1/10 000 (< 0,01 %).

Clinical trials		
MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Eye disorders	Very common	Increased pigmentation of the iris, eye irritation (burning, grittiness, itching, stinging and slight foreign body sensation)
	Common	Blepharitis, eye pain, eyelid oedema, mild to moderate conjunctival hyperaemia, transient punctate epithelial erosions mostly without symptoms
Skin and subcutaneous tissue disorders	Common	Skin rash

Post-Marketing Surveillance	
MedDRA System Organ Class	**Undesirable effects**
Nervous system disorders	Dizziness, headache
Eye disorders	Eyelash and vellus hair changes (increased length, thickness, pigmentation and number), conjunctivitis, vision blurred, iritis/uveitis, keratitis, macular oedema including cystoid macular oedema, symptomatic corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation, periorbital oedema
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

Special precautions:

General:

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

Asthma:

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

There is limited experience of XALATAN in inflammatory ocular conditions, inflammatory, neovascular, angle closure, congenital or pigmentary glaucoma and also in pseudophakic patients with open angle glaucoma.

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

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.

XALATAN 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.

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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if XALATAN is overdosed.

If XALATAN 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 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.

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

If overdosage with XALATAN occurs, treatment should be symptomatic.

IDENTIFICATION:

The solution is a clear, colourless liquid.

PRESENTATION:

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.

STORAGE INSTRUCTIONS:

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**.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

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NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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