

The format of this insert was determined by the Ministry of Health and its content was checked and approved

Xalatan

Ophthalmic Solution brand of latanoprost ophthalmic solution

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xalatan Eye drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of eye drops, solution contains 50 micrograms of latanoprost.

2.5 ml of eye drops, solution (content of a dropper container) contains 125 micrograms of latanoprost.

One drop contains approximately 1.5 micrograms latanoprost.

Excipient: Benzalkonium chloride 0.02% w/v is included as a preservative.

For a 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 as a first line treatment in patients with open angle glaucoma and ocular hypertension.

4.2 Posology and method of administration

Recommended dosage for adults (including the elderly):

Recommended therapy is one eye 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 intraocular pressure lowering effect.

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

As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be compressed at the medial canthus (punctal occlusion) for one minute. This should be performed immediately following the instillation of each drop.

Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.

Latanoprost may be used concomitantly with other classes of topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

4.3 Contraindications

Known hypersensitivity to any component in Xalatan.

4.4 Special warnings and precautions for use

Xalatan 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.

This change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e. blue-brown, grey-brown, yellow-brown and green-brown. In studies with latanoprost, the onset of the change is usually 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 for five years. The effect of increased pigmentation beyond five years has not been evaluated. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation (see section 4.8). During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant color change may be permanent. The iris colour change is slight in the majority of cases and often not observed clinically. The incidence in patients with mixed colour irides ranged from 7 to 85%, with yellow-brown irides having the highest incidence. In patients with homogeneously blue eyes, no change has been observed and in patients with homogeneously grey, green or brown eyes, the change has only rarely been seen.

The colour change is due to increased melanin content in the stromal melanocytes of the iris and not to an increase in 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. No further increase in brown iris pigment has been observed after discontinuation of treatment. It has not been associated with any symptom or pathological changes in clinical trials to date.

Neither naevi nor freckles of the iris have been affected by treatment. Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical trials. Based on 5 years clinical experience, increased iris pigmentation has not been shown to have any negative clinical sequelae and Xalatan can be continued if iris pigmentation ensues. 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. However, patients

should be monitored regularly and if the clinical situation warrants, Xalatan treatment may be discontinued.

There is limited experience of Xalatan in chronic angle closure glaucoma, open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. There is no experience of Xalatan in inflammatory and neovascular glaucoma or inflammatory ocular conditions. 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.

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

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.

Reports of macular oedema including cystoid macular edema have occurred (see section 4.8) mainly in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema (such as diabetic retinopathy and retinal vein occlusion). Xalatan should be used with caution in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.

In patients with known predisposing risk factors for iritis/uveitis, Xalatan 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.

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 and surrounding areas; these changes include increased length, thickness, pigmentation, number of lashes or hairs and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.

Xalatan 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 and is known to discolour soft contact lenses. Close monitoring is required with frequent or prolonged use of Xalatan 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 Xalatan but may be reinserted after 15 minutes (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Definitive drug interaction data are not available.

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.

4.6 Fertility, pregnancy and lactation

Fertility

Latanoprost has not been found to have any effect on male or female fertility in animal studies. (See section 5.3).

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established. It has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate. Therefore, Xalatan should not be used during pregnancy.

Lactation

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

4.7 Effects on ability to drive and use machines

Xalatan has minor or moderate influence on the ability to drive and use machines.

In common with other eye preparations, 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

a. Summary of the safety profile

The majority of adverse events relate to the ocular system. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation (see section 4.4). Other ocular adverse events are generally transient and occur on dose administration.

b. Tabulated list of adverse reactions

Adverse events are categorized by frequency as follows: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$) and very rare ($< 1/10,000$). Not known (cannot be estimated from the available data).

Infections and Infestations:

Not known: Herpetic keratitis

Nervous System Disorders:

Not known: Headache, Dizziness.

Eye Disorders:

Very common: Increased iris pigmentation; mild to moderate conjunctival hyperaemia eye irritation (burning grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes (increased length, thickness, pigmentation and number) (vast majority of reports in Japanese population).

Common: Transient punctate epithelial erosions, mostly without symptoms; blepharitis; eye pain, photophobia.

Uncommon: Eyelid oedema: dry eye; keratitis; vision blurred; conjunctivitis.

Rare: Iritis/uveitis (the majority of reports in patients with concomitant predisposing factors); macular oedema, including cystoid macular edema; symptomatic corneal oedema and erosions; periorbital

oedema; misdirected eyelashes sometimes resulting in eye irritation; extra row of cilia at the aperture of the meibomian glands (distichiasis).

Very rare: Periorbital and lid changes resulting in deepening of the eyelid sulcus.

Not known: iris cyst.

Cardiac Disorders:

Very rare: Unstable angina.

Not known: Palpitations.

Respiratory, Thoracic and Mediastinal Disorders:

Rare: Asthma, asthma aggravation, acute asthma attacks and dyspnoea.

Skin and Subcutaneous Tissue Disorders:

Uncommon: Skin rash.

Rare: Localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids.

Musculoskeletal and Connective Tissue Disorders:

Not known: Myalgia; Arthralgia.

General Disorders and Administration Site Conditions:

Very rare: Non-specific 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.

c. Description of selected adverse reactions

No information is provided.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

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 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 monkeys, latanoprost has been infused intravenously in doses of up to 500 micrograms/kg without major effects on the cardiovascular system.

Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of Xalatan.

If overdosage with Xalatan occurs, treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, prostaglandin analogues.

ATC code: S 01 E E 01 The active substance latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour, primarily through the uveoscleral route and also through the trabecular meshwork. Reduction of the intraocular pressure in man starts about three to four hours after administration and maximum effect is reached after eight to twelve hours. Pressure reduction is maintained for at least 24 hours.

Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in man.

Pivotal studies have demonstrated that Xalatan is effective as monotherapy. In addition, clinical trials investigating combination use have been performed. These include studies that show that latanoprost is effective in combination with beta-adrenergic antagonists (timolol). Short-term (1 or 2 weeks) studies suggest that the effect of latanoprost is additive in combination with adrenergic agonists (dipivalyl epinephrine), oral carbonic anhydrase inhibitors (acetazolamide) and at least partly additive with cholinergic agonists (pilocarpine).

Clinical trials have shown that latanoprost has no significant effect on the production of aqueous humour. Latanoprost has not been found to have any effect on the blood-aqueous barrier.

Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys. However, mild to moderate conjunctival or episcleral hyperaemia may occur during topical treatment.

Chronic treatment with latanoprost in monkey eyes, which had undergone extracapsular lens extraction, did not affect the retinal blood vessels as determined by fluorescein angiography.

Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term treatment.

Latanoprost in clinical doses has not been found to have any significant pharmacological effects on the cardiovascular or respiratory system.

5.2 Pharmacokinetic properties

Latanoprost (mw 432.58) is an isopropyl ester prodrug which per se is inactive, but after hydrolysis to the acid of latanoprost becomes biologically active.

Absorption

The prodrug is well absorbed through the cornea and all drug that enters the aqueous humour is hydrolysed during the passage 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 humor during the first four hours, and in plasma only during the first hour after local administration.

Metabolism:

Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β -oxidation.

Excretion:

The elimination of the acid of latanoprost from human plasma is rapid ($t_{1/2}=17$ min) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β -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.

5.3 Preclinical safety data*Systemic/Ocular Effects:*

The ocular as well as systemic toxicity of latanoprost has been investigated in several animal species. Generally, latanoprost is well tolerated with a safety margin between clinical ocular dose and systemic toxicity of at least 1000 times. High doses of latanoprost, approximately 100 times the clinical dose/kg body weight, administered intravenously to unanaesthetised monkeys have been shown to increase the respiration rate probably reflecting bronchoconstriction of short duration. In monkeys, latanoprost has been infused intravenously in doses of up to 500 mcg/kg without major effects on the cardiovascular system. In animal studies, latanoprost has not been found to have sensitising properties.

In the eye, no toxic effects have been detected with doses of up to 100 micrograms/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 micrograms/eye/day). In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris.

Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys.

The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris with no proliferative changes observed. The change in iris colour may be permanent.

In chronic ocular toxicity studies, administration of latanoprost 6 micrograms/eye/day has also been shown to induce increased palpebral fissure. This effect is reversible and occurs at doses above the clinical dose level. The effect has not been seen in humans.

Carcinogenesis:

Carcinogenicity studies in mice and rats were negative.

Mutagenesis:

Latanoprost was found negative in reverse mutation tests in bacteria, gene mutation in mouse lymphoma and mouse micronucleus test. Chromosome aberrations were observed in vitro with human

lymphocytes. Similar effects were observed with prostaglandin $F_{2\alpha}$, a naturally occurring prostaglandin, and indicates that this is a class effect.

Additional mutagenicity studies on in vitro/in vivo unscheduled DNA synthesis in rats were negative and indicate that latanoprost does not have mutagenic potency.

Impairment of Fertility:

Latanoprost has not been found to have any effect on male or female fertility in animal studies. In the embryotoxicity study in rats, no embryotoxicity was observed at intravenous doses (5, 50 and 250 micrograms/kg/day) of latanoprost. However, latanoprost induced embryo-lethal effects in rabbits at doses of 5 micrograms/kg/day and above.

The dose of 5 micrograms/kg/day (approximately 100 times the clinical dose) caused significant embryo-fetal toxicity characterised by increased incidence of late resorption and abortion and by reduced foetal weight.

Teratogenesis:

No teratogenic potential has been detected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Benzalkonium chloride
Sodium dihydrogen phosphate monohydrate
Disodium phosphate anhydrous
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 drugs 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.

After first opening of container: 4 weeks.

6.4 Special precautions for storage

Protect from light. Store unopened bottle(s) under refrigeration at 2° to 8°C. Once a bottle is opened for use, it may be stored at room temperature up to 25°C for 4 weeks.

6.5 Instructions for use and handling

No special requirements.

6.6 How supplied

XALATAN Sterile Ophthalmic Solution is a clear, isotonic, buffered, preserved colorless solution of latanoprost 0.005% (50 µg/mL). It is supplied as a 2.5 mL solution in a 5 mL clear low density polyethylene bottle with a clear low density polyethylene dropper tip, a turquoise high density polyethylene screw cap, and a tamper-evident clear low density polyethylene overcap.

2.5 mL fill, 0.005% (50 µg/mL)

7. Manufacturer:

Pfizer Manufacturing Belgium NV/SA, PUURS, Belgium.

License holder:

Pfizer Pharmaceuticals Israel Ltd.,
9 Shenkar St, Herzliya Pituach, 46725