Xalaprost

Latanoprost

NAME OF THE MEDICAL PRODUCT

Xalaprost 0.005%w/v Eye Drops

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 50mcg of latanoprost.

One drop contains approximately 1.5 mcg latanoprost.

PHARMACEUTICAL FORM

Eye drop solution.

The solution is a clear, colourless liquid.

CLINICAL PARTICULARS

Therapeutic Indications

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

Reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma.

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 Xalaprost is administered in the evening.

The dosage of Xalaprost 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.

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

If more than one topical ophthalmic medicinal product is being used, the medicinal products should be administered at least five minutes apart.

Paediatric population:

Xalaprost 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 are very limited *(see Pharmacodynamics Properties).*

Contraindications

Hypersensitivity to the active substance or to any other component of the product.

Special Warnings and Precautions for Use

Xalaprost 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. The onset of the change is usually within the first few months of treatment, rarely during the following year of treatment. Some patients is developed iris pigmentation *(see Undesirable Effects)* however the rate of progression of iris pigmentation decreases with time. The iris colour change is slight in the majority of cases and often not been observed. The highest incidence in patients with mixed colour irides is patients with yellow-brown irides. 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.

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. Increased iris pigmentation has not been shown to have any negative clinical sequelae and Xalaprost can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, Xalaprost treatment may be discontinued.

There is limited experience of Xalaprost in chronic angle closure glaucoma, open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. There is no experience of Xalaprost in inflammatory and neovascular glaucoma, inflammatory ocular conditions, or congenital glaucoma. Xalaprost 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 Xalaprost should be used with caution in these conditions until more experience is obtained.

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

Xalaprost 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 have occurred *(see Undesirable Effects)* 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). Xalaprost 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, Xalaprost can be used with caution.

Some patients with asthma is reported of exacerbation of asthma and/or dyspnoea, therefore asthmatic patients should be treated with caution until there is sufficient experience, see also section Undesirable Effects.

Periorbital skin discolouration is not permanent and in some patient has reversed while continuing treatment with Xalaprost.

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.

This medicinal product contains benzalkonium chloride which is commonly used as a preservative in ophthalmic products. Contact lenses may absorb benzalkonium chloride and these should be removed before applying Xalaprost but may be reinserted after 15 minutes *(see Posology and Method of Administration).*

Paediatric population

Efficacy and safety data in the age group < 1 year are very limited *(see Pharmacodynamics Properties)*. No data are available for preterm infants (less than 36 weeks gestational age).

In children from 0 to < 3 years old that mainly suffers from PCG (Primary Congenital Glaucoma), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment.

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

Interactions

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.

Paediatric population

Interaction studies have only been performed in adults.

Fertility, Pregnancy and Lactation

Fertility

Latanoprost has not been found to have any effect on male or female fertility in animal studies.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Latanoprost should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

Latanoprost and its metabolites may pass into breast milk. Xalaprost should therefore be used with caution in nursing women.

Effects on 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.

Undesirable Effects

The majority of adverse events relate to the ocular system, some patients is developed iris pigmentation *(see Special Warnings and Precautions for Use)*. Other ocular adverse events are generally transient and occur on dose administration.

Adverse events are listed as follows:

Infections and Infestations:

Herpetic keratitis

Eye Disorders:

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); transient punctate epithelial erosions, mostly without symptoms; blepharitis; eye pain; eyelid oedema: dry eye; keratitis; vision blurred; conjunctivitis; Iritis/uveitis; macular oedema; 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); photophobia; periorbital and lid changes resulting in deepening of the eyelid sulcus; iris cyst

Nervous System Disorders:

Headache, Dizziness.

Cardiac Disorders:

Aggravation of angina in patients with pre-existing disease; Palpitations.

Respiratory, Thoracic and Mediastinal Disorders:

Asthma, asthma exacerbation and dyspnoea.

Skin and Subcutaneous Tissue Disorders:

Skin rash; Localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids.

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

The safety profile in paediatric patients 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 Pharmacodynamics Properties)*. Adverse events seen more frequently in the paediatric population as compared to adults are: nasopharyngitis and pyrexia.

Overdose

Apart from ocular irritation and conjunctival hyperemia, no other ocular adverse effects are known if latanoprost is overdosed.

If latanoprost is accidentally ingested the following information may be useful: One 2.5 ml bottle contains 125 micrograms latanoprost. More than 90% is metabolized during the first pass through the liver. Intravenous infusion of 3 mcg/kg in healthy volunteers induced no symptoms, but a dose of 5.5 - 10 mcg/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. 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 latanoprost.

If overdosage with latanoprost occurs, treatment should be symptomatic.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics Properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, prostaglandin analogues, ATC code: S01EE01

Latanoprost, a selective prostaglandin F2α analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour. 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.

The main mechanism of action is increased uveoscleral outflow, although in some case it is increase in outflow facility (decrease in outflow resistance).

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, however mild to moderate conjunctival or episcleral hyperaemia may occur during topical treatment.

Chronic treatment with latanoprost which had undergone extracapsular lens extraction did not affect the retinal blood vessels.

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

Latanoprost has not been found to have any significant pharmacological effects on the cardiovascular or respiratory systems.

Paediatric population

The efficacy of latanoprost in paediatric patients ≤18 years of age is compared with timolol in patients diagnosed with ocular hypertension and paediatric glaucoma. Neonates were required to be at least 36 weeks gestational age. Patients received either latanoprost 0.005% once daily or timolol 0.5% (or optionally 0.25% for subjects younger than 3 years old) twice daily. The primary efficacy endpoint was the mean reduction in intraocular pressure at Week 12. Mean intraocular pressure reductions in the latanoprost and timolol groups were similar. In all age groups (0 to <3 years, 3 to <12 years and 12 to 18 years of age) the mean intraocular pressure reduction at Week 12 in the latanoprost group was similar to that in the timolol group. Nevertheless, efficacy data in the age group 0 - < 3 year old were based on only latanoprost and no relevant efficacy was shown from the age group 0 -< 1 year old. No data are available for preterm infants (less than 36 weeks gestational age).

Intraocular pressure reductions among subjects in the primary congenital/infantile glaucoma (PCG) subgroup were similar between the latanoprost group and the timolol group. The non-PCG (e.g. juvenile open angle glaucoma, aphakic glaucoma) subgroup showed similar results as the PCG subgroup.

Pharmacokinetics 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.

The prodrug is well absorbed through the cornea and all drug that enters the aqueous humour is hydrolysed during the passage through the cornea.

The peak concentration in the aqueous humour is reached about two hours after topical administration. After topical application, latanoprost is distributed primarily in the anterior segment, the conjunctivae and the eyelids. Only minute quantities of the drug reach the posterior segment.

There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. The half life in plasma is 17 minutes. 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.

Paediatric population

In pharmacokinetic study of plasma latanoprost acid concentrations, adults and paediatric patients (from birth to < 18 years of age) with ocular hypertension and glaucoma 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 Overdose)*. 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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Benzalkonium Chloride

Sodium Chloride

Disodium phosphate anhydrous

Sodium dihydrogen phosphate monohydrate

Sodium hydroxide solution

Hydrochloric acid solution

Water for injection

Incompatibilities

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

Shelf life

Please refer to outer carton for shelf life.

Storage Conditions

Store unopened bottle at 2°C to 8°C.
Once a bottle is opened for use, stored below 25°C for 4 weeks.
Protect from light.

Nature and Contents of Container

Each bottle contains 2.5 mL eye drops corresponding to a minimum of 80 drops of solution. One drop contains approximately 1.5 mcg latanoprost.

NAME AND ADDRESS OF MANUFACTURER

RAFARM SA
Agiou Louka Str,
Thesi Pousi-Xatzi,
19002 Paiania, Attiki,
Greece.

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