1. NAME OF THE MEDICINAL PRODUCT

Xylase DZ Eye Drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre contains 0.05mg of Latanoprost + 2mg of Dorzolamide

3. PHARMACEUTICAL FORM

Eye drops, Solution.

Clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The combination of latanoprost and dorzolamide is indicated for the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. This dual therapy is used when monotherapy (a single medication) fails to lower eye pressure to the target level.

4.2 Posology and method of administration

Posology

Adults

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 Xylase DZ eye drop is administered in the evening.

The dosage of Xylase DZ eye drop 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.

Method of administration

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.

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

Pediatric population

Xylase DZ eye drops may be used in pediatric patients at the same posology as in adults. No data are available for pre-term infants (less than 36 weeks gestational age). Data in the age group < 1 year (4 patients) are limited (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substances (Latanoprost and Dorzolamide)

4.4 Special warnings and precautions for use

Xylase DZ eye drops 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 clinical studies with Xylase DZ eye drops, the onset of the change is usually within the first 8 months 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 Xylase DZ eye drops safety study, 33% of patients developed iris pigmentation (see section 4.8). 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 Xylase DZ eye drops can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, Xylase DZ eye drops treatment may be discontinued.

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

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

Xylase DZ eye drops 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 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). Xylase DZ eye drops 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, Xylase DZ eye drops 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).

Periorbital skin discolouration has been observed, the majority of reports being in Japanese patients. Experience to date shows that periorbital skin discolouration is not permanent and in some cases has reversed while continuing treatment with Xylase DZ.

Xylase DZ 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.

Xylase DZ eye drops 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 Xylase DZ eye drops 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 Xylase DZ eye drops 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.

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4.6 Pregnancy and lactation

Fertility

Latanoprost + Dorzolamide 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, Latanoprost + Dorzolamide eye drops should not be used during pregnancy.

Breast-feeding

Latanoprost + Dorzolamide and its metabolites may pass into breast milk and Latanoprost eye drops should therefore not be used in nursing women or breast feeding should be stopped.

4.7 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.

4.8 Undesirable effects

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 keratitis, 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; 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 exacerbation 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:*	Chest pain.

4.9 Overdose

Symptoms

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

If Latanoprost eye drops 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 latanoprost.

If overdosage with Latanoprost eye drops occurs, treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Prostaglandin analogues

ATC code: X01EE52

The active substance latanoprost, a 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 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 latanoprost 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.

Pediatric population

The efficacy of Latanoprost in pediatric patients ≤ 18 years of age was demonstrated in a 12-week, double-masked clinical study of latanoprost compared with timolol in 107 patients diagnosed with ocular hypertension and pediatric glaucoma. Neonates were required to be at least 36 weeks gestational age. Patients received at random either latanoprost 50 mcg/ml 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 (IOP) from baseline at Week 12 of the study. Mean IOP reductions in the latanoprost and timolol groups were similar. In all age groups studied (0 to <3 years, 3 to < 12 years and 12 to 18 years of age) the mean IOP reduction at Week 12 in the latanoprost group was similar to that in the timolol group. Nevertheless, efficacy data in the age group 0 to < 3 years were based on only 13 patients for latanoprost and no relevant efficacy was shown from the 4 patients representing the age group 0 to < 1 year old in the clinical pediatric study. No data are available for preterm infants (less than 36 weeks gestational age).

IOP 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.

The effect on IOP was seen after the first week of treatment (see table) and was maintained throughout the 12 week period of study, as in adults.

Table: IOP reduction (mmHg) at week 12 by active treatment group and baseline diagnosis				
	Latanoprost N=53		**Timolol N=54**	
Baseline Mean (SE)	27.3 (0.75)		27.8 (0.84)	
Week 12 Change from Baseline Mean[†](SE)	-7.18 (0.81)		-5.72 (0.81)	
p-value vs. timolol	0.2056			
	PCG N=28	**Non-PCG N=25**	**PCG N=26**	**Non-PCG N=28**
Baseline Mean (SE)	26.5 (0.72)	28.2 (1.37)	26.3 (0.95)	29.1 (1.33)
Week 12 Change from Baseline Mean[†](SE)	-5.90 (0.98)	-8.66 (1.25)	-5.34 (1.02)	-6.02 (1.18)
p-value vs. timolol	0.6957	0.1317		

SE: standard error.

[†] Adjusted estimate based on an analysis of covariance (ANCOVA) model.

Dorzolamide

Mechanism of action

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. In humans, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II) found primarily in red blood cells (RBCs) but also in other tissues. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion. The result is a reduction in intra-ocular pressure (IOP).

Dorzolamide 20mg/ml Eye Drops Solution contains dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, dorzolamide reduces elevated intra-ocular pressure, whether or not associated with glaucoma. Elevated intra• ocular pressure is a major risk factor in the pathogenesis of optic nerve damage and visual-field loss. Dorzolamide does not cause pupillary constriction and reduces intra-ocular pressure without side effects such as night blindness, accommodative spasm. Dorzolamide has minimal or no effect on pulse rate or blood pressure.

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.

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. After topical application in monkeys, 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 in man. The main metabolites, the 1,2-dinor and 1,2,3,4-tetranor metabolites, exert no or only weak biological activity in animal studies and are excreted primarily in the urine.

Pediatric population

An open-label pharmacokinetic study of plasma latanoprost acid concentrations was undertaken in 22 adults and 25 pediatric patients (from birth to < 18 years of age) with ocular hypertension and glaucoma. All age groups were treated with latanoprost 50 mcg/ml, 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 pediatric and adult patients, and resulted in no accumulation of latanoprost acid in the systemic circulation under steady-state conditions.

5.3 Preclinical safety data

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 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.

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.

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 F2α, 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. Carcinogenicity studies in mice and rats were negative.

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 embryolethal 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 embryofetal toxicity characterised by increased incidence of late resorption and abortion and by reduced fetal weight.

No teratogenic potential has been detected.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

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6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

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6.4 Special precautions for storage

Store in the original package.

Store below 30°C. Keep medicine away from direct sunlight

Keep all medicine out of the reach of children.

6.5 Nature and contents of container

2.5ml dropper bottle placed in an inner carton with insert

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER AND MANUFACTURER

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