XALATAN
Latanoprost 0.005% Solution

1. NAME OF THE MEDICINAL PRODUCT

XALATAN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 50 mcg of latanoprost.
One drop contains approximately 1.5 mcg of latanoprost.
Excipient with known effect: benzalkonium chloride.

3. PHARMACEUTICAL FORM

Ophthalmic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension. It may also be used for the reduction of elevated intraocular pressure as an adjunct medical therapy in patients with primary chronic angle closure glaucoma.

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

4.2 Posology and method of administration

Use in adults (including the elderly)
One drop in the affected eye(s) once daily. Optimal effect is obtained if latanoprost is administered in the evening.

The dosage of latanoprost should not exceed once daily since it has been shown that more frequent administration decreases the IOP lowering effect.

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

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.

Contact lenses should be removed before instillation of the eye drops and may be reinserted after fifteen minutes (see section **4.4**).

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 are limited (see section **5.1**).

4.3 Contraindications

Known hypersensitivity to latanoprost or any other component of the product.

4.4 Special warnings and special precautions for use

Iris pigmentation changes
Latanoprost may gradually change the 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 heterochromia.

This change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e., blue-brown, grey-brown, green-brown and yellow-brown. The highest incidence was found in patients with green-brown and yellow-brown irides. In patients with homogeneously blue eyes, no change has been observed and in patients with homogenously grey, green or brown eyes, the change has only rarely been seen. The onset of the change is usually within the first eight months of treatment, but may occur later in a small number of patients.

The colour change is due to increased melanin content in the stromal melanocytes of the iris and not to an increase in the 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. Patients who develop increased iris pigmentation should be examined regularly and, depending on the clinical situation, treatment may be stopped. No further increase in brown iris pigment has been observed after discontinuation of treatment, but the resultant colour change may be permanent. It has not been associated with any symptom or pathological changes in clinical trials of up to 48 months duration.

Naevi or freckles of the iris have not been affected by treatment.

Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in long term 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 latanoprost 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 latanoprost 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.

The potential for heterochromia exists for patients receiving unilateral treatment.

In a long-term observational paediatric study evaluating hyperpigmentation changes in the eye among patients with paediatric glaucoma, iris colour darkening and localised iris pigmentation were observed to a slightly greater extent in patients exposed to latanoprost group compared with the unexposed group (see section **5.1**).

Eyelid and eyelash changes
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; 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.

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

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

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

Caution is recommended when using latanoprost 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, latanoprost should be used with caution.

There is no experience in patients with severe or brittle asthma. Such patients should therefore be treated with caution until there is sufficient experience.

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 latanoprost.

Herpetic keratitis
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.

Paediatric population
Efficacy and safety data in the age group <1 year are 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 suffers from PCG (Primary Congenital Glaucoma), surgery (e.g., trabeculotomy/goniotomy) remains the first line treatment.

Contact lenses
This product contains benzalkonium chloride, which may be absorbed by contact lenses (see section **4.2**).

4.5 Interaction with other medicinal products and other forms of interaction

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.

Paediatric population
Interaction studies have only been performed in adults.

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
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 (see section **5.3**).

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

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

Table 1: Latanoprost Adverse Drug Reaction Table

System Organ Class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Frequency Not Known (cannot be estimated from available data)
Infections and infestations				Herpetic keratitis*
Nervous system disorders		Dizziness*; headache*		
Eye disorders	Eye irritation (burning, grittiness, itching, stinging and foreign body sensation); eye pain; eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes)*; ocular hyperaemia; iris hyperpigmentation; blepharitis; conjunctivitis*	Macular oedema including cystoid macular oedema*; photophobia*; eyelid oedema; keratitis*; uveitis*	Corneal oedema*; iritis*	Punctate keratitis*; corneal erosion*; trichiasis*; vision blurred*; periorbital and lid changes resulting in deepening of the eyelid sulcus*; darkening of the palpebral skin of the eyelids*; localised skin reaction on the eyelids*; iris cyst*; pseudopemphigoid of the ocular conjunctiva*
Cardiac disorders		Angina; palpitations*		Angina unstable*
Respiratory, thoracic and mediastinal disorders		Asthma*; dyspnoea*		Asthma aggravation*; acute asthma attacks*
Gastrointestinal disorders		Nausea*	Vomiting*	
Skin and subcutaneous tissue disorders		Rash	Pruritus	
Musculoskeletal and connective tissue disorders		Myalgia*; arthralgia*		
General disorders and administration site conditions		Chest pain*		

*ADR identified post-marketing

Adverse reactions reported with the use of eyedrops containing phosphate buffers
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.

In a long-term observational paediatric study involving 115 patients, the safety profile was consistent with that reported in previous paediatric studies and no new adverse events were identified (see section **5.1**).

4.9 Overdose

If overdosage with latanoprost occurs, treatment should be symptomatic.

Apart from ocular irritation and conjunctival hyperaemia, 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 metabolised 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 (see section **5.3**).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The active substance latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a selective prostanoid FP receptor agonist that reduces the IOP 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.

Pivotal studies have demonstrated that Xalatan is effective as a 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.

Clinical studies of latanoprost in primary chronic angle closure glaucoma have been limited to 12 weeks. Clinical efficacy and safety in patients with primary chronic angle glaucoma have not been established beyond 12 weeks.

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.

United Kingdom Glaucoma Treatment Study
The published United Kingdom Glaucoma Treatment Study (UKGTS) involving a randomised, triple-masked placebo-controlled trial was conducted to evaluate the efficacy of latanoprost 0.005% (50 mcg/mL) eye drops, in preserving visual function in individuals with newly diagnosed open-angle glaucoma (OAG).

Five-hundred and sixteen patients with newly diagnosed OAG were enrolled; 258 in the latanoprost group who received latanoprost 0.005% (50 mcg/mL) eye drops and 258 in the control group who received placebo (latanoprost vehicle eye drops). Drops were administered from identical bottles, once a day, to both eyes. The mean age of the patients was 66 years, 52.9% were male; 90.1% of the patients were white, and approximately one third (32.2%) reported a family history of glaucoma. The patients were monitored by visual field (VF) testing, quantitative imaging, optic disc photography, and tonometry during 11 visits over 2 years. The primary outcome measure was time to VF deterioration within 24 months.

The baseline mean IOP was 19.6 mmHg in the latanoprost group and 20.1 mmHg in controls. The primary outcome data was analyzed for 461 patients (231 in the latanoprost group and 230 in the placebo group). At 24 months endpoint, 94 patients had VF deterioration consistent with glaucomatous progression: 59 patients (25.6%; 95% CI 20.1-31.8) in the placebo group compared with 35 patients (15.2%; 95% CI 10.8-20.4) in the latanoprost group (p=0.006) associated with IOP reduction from baseline of 3.8 mmHg in the latanoprost group and 0.9 mmHg in the placebo group (after last observation carried forward adjustment). It was observed that, the time to first deterioration was significantly longer in the latanoprost group than in the placebo group (adjusted HR 0.44, 95% CI 0.28-0.69; p=0.0003).

Paediatric population
The efficacy of Xalatan in paediatric 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 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 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 paediatric 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 and was maintained throughout the 12-week period of study, as in adults (see table 2).

Table 2: 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 analysis of covariance (ANCOVA) model				

Two non-interventional (NI) long term, post-authorisation safety studies (PASS) were designed to describe the incidence rate of hyperpigmentation changes of the eye over a total of 10 years of follow-up by combining data collected during the 3-year period of the study and the extended 7-year follow-up study among paediatric patients with glaucoma or elevated IOP. A total of 115 patients were transitioned from the parent study and were part of the Full Analysis Set (FAS). Study eligible patients (< 18 years) were categorised into 3 groups: 76 patients in latanoprost group (continuously treated with latanoprost for ≥ 1 month); 1 patient in non-latanoprost prostaglandin analogues (PGA) group (continuously treated with non-latanoprost PGA for ≥ 1 month); and 38 in PGA unexposed (not treated continuously with any PGA for ≥ 1 month). The study result indicated that hyperpigmentation changes of the eye were observed in only a small number of patients in both treatment groups, with greater rate in the latanoprost exposed group than in the PGA unexposed group. Eyelash hyperpigmentation rates were 4.5% vs 0% and iris hyperpigmentation rates were 6.0% vs 3.0% in latanoprost exposed group and PGA unexposed group respectively. The incidence rates (per 100 patient years) of hyperpigmentation changes in the eye were low and comparable in both treatment groups: eyelash lengthening 2.53 versus 3.35, iris hyperpigmentation 0.92 versus 0.42, and eyelash hyperpigmentation: 0.69 versus none.

No serious adverse events (SAEs) were considered related to study treatment. The majority of treatment emergent adverse events (TEAEs) reported were in the system organ class of eye disorders, which were mostly mild and more frequently reported in the latanoprost exposed group than in the PGA unexposed group. No clinically significant safety issues or new safety issues/different frequencies of adverse events (AEs) were

identified compared to the existing safety profile. Overall, the rates of safety endpoints observed in this study are comparable to the AE rates reported in previous paediatric studies.

5.2 Pharmacokinetic properties

Absorption
Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolysed to the acid form to become biologically active. 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 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.

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.

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

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 indicate 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 embryolethal effects in rabbits at doses of 5 micrograms/kg/day and above. Latanoprost has been shown to cause embryofetal toxicity in rabbits characterised by increased incidences of late resorption and abortion and reduced fetal weight when given in intravenous doses approximately 100 times the human dose.

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, and water for injection.

6.2 Incompatibilities

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

6.3 Shelf-life

Shelf-life: 3 years.

Shelf-life after opening container: 4 weeks.

6.4 Special precautions for storage

Store unopened bottle under refrigeration at 2°C to 8°C (36°F to 46°F).

When a bottle is opened for use, it may be stored at room temperature up to 25°C (77°F) for 4 weeks.

Protect from light.

6.5 Nature and contents of container

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

7. PRODUCT OWNER

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