Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Xalatan 50 micrograms/mL Eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL Eye drops solution contains 50 micrograms of latanoprost.

One drop contains approximately 1.5 micrograms latanoprost.

Excipient with known effect
Benzalkonium chloride 0.2 mg/mL is included as a preservative.
Sodium dihydrogen phosphate monohydrate (E339i) 7.70 mg/mL.
Disodium phosphate anhydrous (E339ii) 1.55 mg/mL.

For the 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 (IOP) in patients with open angle glaucoma and ocular hypertension in adults (including the elderly).

Reduction of elevated IOP in paediatric patients with elevated IOP and paediatric glaucoma.

4.2 Posology and method of administration

Posology

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 IOP lowering effect.

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

Paediatric population
Xalatan Eye drops, solution 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).

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 medicinal product is being used, the medicinal products should be administered at least five minutes apart.

4.3 Contraindications

Hypersensitivity to latanoprost or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Iris pigmentation changes
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 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 latanoprost 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.

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).

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. 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 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.

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 Xalatan.

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.

Preservative
Xalatan contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

Contact lenses
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).

Paediatric population
Efficacy and safety data in the age group < 1 year are very 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 suffer from primary congenital glaucoma(PCG), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment.

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 IOP 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.

4.6 Fertility, pregnancy and lactation

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

Breast-feeding
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.

Fertility

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

4.7 Effects on ability to drive and use machines

Xalatan has minor 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 reactions 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 reactions are generally transient and occur on dose administration.

b. Tabulated list of adverse reactions

Adverse reactions are categorized by frequency as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (frequency cannot be estimated from the available data).

System Organ Class		**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**
Infections and infestations					Herpetic keratitis*§	
Nervous system disorders				Headache*; dizziness*		
Eye disorders		Iris hyperpigmentation; mild to moderate conjunctival hyperaemia; eye irritation (burning grittiness, itching, stinging andforeign body sensation); eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation and number of eyelashes)	Punctate keratitis, mostly without symptoms; blepharitis; eye pain; photophobia; conjunctivitis*	Eyelid oedema; dry eye; keratitis*; vision blurred; macular oedema including cystoid macular oedema*; uveitis*	Iritis*; corneal oedema*; corneal erosion; periorbital oedema; trichiasis*; distichiasis; iris cyst*§; localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids; pseudopemphigoid of ocular conjunctiva*§	Periorbital and lid changes resulting in deepening of the eyelid sulcus
Cardiac disorders				Angina; palpitations*		Angina unstable
Respiratory, thoracic and mediastinal disorders				Asthma*; dyspnoea*	Asthma exacerbation	
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

§ADR frequency estimated using "The Rule of 3"

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.

d. Paediatric population

In two short term clinical trials (≤ 12 weeks), involving 93 (25 and 68) paediatric patients the safety profile was similar to thatin adults and no new adverse events were identified.
The short-termsafety 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).

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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

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

Treatment
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: Ophthalmologicals; Antiglaucoma preparations and miotics, prostaglandin analogues. ATC code: S 01 E E 01
The active substance latanoprost, a prostaglandin F_{2a}analogue, is a selective prostanoid FP receptor agonist which reduces the IOP by increasing the outflow of aqueous humour. Reduction of the IOP 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.

The published United Kingdom Glaucoma Treatment Study (UKGTS), a randomised, triple-masked placebo-controlled trial, evaluated the efficacy of latanoprost (50 mcg/mL) eye drops, in preserving visual field in 516 patients with newly diagnosed mild to moderate open-angle glaucoma (OAG). Fifty-nine patients (25.6%; 95% CI 20.1-31.8) in the placebo group had visual field deterioration consistent with glaucoma 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). 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). Despite early trial termination after interim analysis based on primary outcome of time to event, and the potential limitation of high loss to follow-up of patients, the study showed that lowering IOP with latanoprost delayed visual field deterioration in some patients with mild to moderate open-angle glaucoma.

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 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 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 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.

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 (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.

Distribution
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.

Biotransformation and elimination
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.

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 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 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

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 1,000 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 $F_{2\alpha}$, a naturally occurring prostaglandin, and indicates that this is a class effect.

Additional mutagenicity studies on i*n 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 embryofoetal toxicity characterised by increased incidence of late resorption and abortion and by reduced foetal weight.

No teratogenic potential has been detected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Benzalkonium chloride
Sodium dihydrogen phosphate monohydrate (E339i)

Disodium phosphate anhydrous (E339ii)
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 medicinal products are used, the eye drops should be administered with an interval of at least five minutes.

6.3 Shelf life

Before first opening: 2 years

After first opening of container: 4 weeks

6.4 Special precautions for storage

Do not store above 25°C

After first opening: Use within 4 weeks (see section 6.3).

Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

Dropper container (5 mL) of polyethylene with a screw cap and tamper evident overcap of polyethylene.

Each dropper container contains 2.5 mL Eye drops, solution corresponding to approximately 80 drops of solution.

Pack sizes: 1 x 2.5 mL, 3 x 2.5 mL, 6 x 2.5 mL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Upjohn EESV
Rivium Westlaan 142
2909 LD Capelle aan den IJssel
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA23055/009/001

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