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For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Latanoprost Eye Drops I.P.
XALATAN®

PAA206348
0058

1. NAME(S) 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.

3. PHARMACEUTICAL FORM
Ophthalmic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma, chronic angle closure glaucoma, and ocular hypertension.
Reduction of elevated intraocular pressure in paediatric patients with elevated intraocular pressure and paediatric glaucoma.

4.2 Posology and Method of Administration
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 intraocular pressure lowering effect.
If one dose is missed, treatment should continue with the next dose as normal.
As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrimal sac be compressed at the medial canthus (punctal occlusion) for one minute. This should be performed immediately following the instillation of each drop.
Latanoprost may be used concomitantly with other classes of topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic medicinal product is being used, the medicinal products 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 Special Warnings and Special Precautions for Use** – **General**).
Pediatric 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 (4 patients) are limited (see section **5.1 Pharmacodynamic Properties**).

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

4.4 Special Warnings and Special Precautions for Use
General:
This product contains benzalkonium chloride, which may be absorbed by contact lenses (see section **4.2 Posology and Method of Administration**).
Ocular:
Latanoprost may gradually increase the brown pigment of the iris. The eye color change is due to increased melanin content in the stromal melanocytes of the iris, rather than to an increase in the number of melanocytes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. The change in iris color is mild in the majority of cases and may not be detected clinically. The increase in iris pigmentation in one or both eyes has been documented predominantly in patients who have mixed-colored irides that contain the color brown at baseline. Neither nevi nor freckles of the iris have been affected by treatment. No accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has been observed in 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 color change may be permanent.
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.
The potential for heterochromia exists for patients receiving unilateral treatment.
Macular edema, including cystoid macular edema, 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 edema. Caution is recommended when using latanoprost in these patients.
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 Undesirable Effects**.
There is limited experience with latanoprost in the treatment of inflammatory neovascular or congenital glaucoma. Therefore, it is recommended that latanoprost should be used with caution in these conditions until more experience is obtained.
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.
Xalatan contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, may cause eye irritation and is known to discolour soft contact lenses. Close monitoring is required with frequent or prolonged use of Xalatan in dry eye patients, or in conditions where the cornea is compromised. Contact lenses may absorb benzalkonium chloride and these should be removed before applying Xalatan but may be reinserted after 15 minutes (see section **4.2 Posology and Method of Administration**).

Paediatric Population
Efficacy and safety data in the age group <1 year (4 patients) are very limited (see section **5.1 Pharmacodynamic 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 Primary Congenital Glaucoma (PCG), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment.
Long-term safety in children has not yet been established.

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 Preclinical Safety Data** – *Impairment of Fertility*).
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 Preclinical Safety Data** – *Impairment of Fertility*).
Breast-feeding:
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
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 Special Warnings and Special Precautions for Use**). Other ocular adverse reactions are generally transient and occur on dose administration.
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	Commo n ≥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 and foreign 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; photophob ia; conjunctiv itis*	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; pseudopemphig oid 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"

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 Pharmacodynamic Properties**). Adverse events seen more frequently in the paediatric population as compared to adults are: nasopharyngitis and pyrexia.
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.

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VIATRIS

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Superseded Affiliate Item Code	N/A	Vendor Job No.	108658629/0106
TrackWise/GLAMS Job No.	3074728	Artwork Proof No.	2
MA No.	IL/FF-000647-RC/FF-002306	Client Market	India
Packing Site/Printer	Pfizer Manufacturing Puurs (Puurs - BE)	Keyline/Drawing No.	I028_05/F
New Supplier Code	PAA206348	Barcode Info	N/A
Superseded Supplier Code	PAA103920	3D Render ID	N/A
Supplier SAP No.	N/A	Source code	0058
Sign-offs			

No. of colours	1	Page Count	1 of 2
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Non-Print Colours	Keyline		
Equate CMYK with			
Main Font	Helvetica Neue LT Pro	Body Text Size	7 pt
Dimensions	105 x 520 mm	Min Text Size used	7 pt

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

4.9 Overdose
Apart from ocular irritation and conjunctival 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 mcg 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 (see section **5.3 Preclinical Safety Data** – *Systemic/Ocular Effects*).
If overdosage with latanoprost occurs, treatment should be symptomatic.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Antiglaucoma preparations and miotics, prostaglandin analogues ATC code: S 01 E E 01
The active substance latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a selective prostanoid FP receptor agonist that reduces the intraocular pressure by increasing the outflow of aqueous humor, primarily through the uveoscleral route and also through the trabecular meshwork. Reduction of the intraocular pressure in man starts about three to four hours after administration and maximum effect is reached after eight to twelve hours. Pressure reduction is maintained for at least 24 hours.
Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in man.
Pivotal studies have demonstrated that Xalatan is effective as monotherapy. In addition, clinical trials investigating combination use have been performed. These include studies that show that latanoprost is effective in combination with beta-adrenergic antagonists (timolol). Short-term (1 or 2 weeks) studies suggest that the effect of latanoprost is additive in combination with adrenergic agonists (dipivalyl epinephrine), oral carbonic anhydrase inhibitors (acetazolamide) and at least partly additive with cholinergic agonists (pilocarpine).
Clinical trials have shown that latanoprost has no significant effect on the production of aqueous humour. Latanoprost has not been found to have any effect on the blood-aqueous barrier.
Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys. However, mild to moderate conjunctival or episcleral hyperaemia may occur during topical treatment.
Chronic treatment with latanoprost in monkey eyes, which had undergone extracapsular lens extraction, did not affect the retinal blood vessels as determined by fluorescein angiography.
Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term treatment.
Latanoprost in clinical doses has not been found to have any significant pharmacological effects on the cardiovascular or respiratory system.
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 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 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.

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.

5.2 Pharmacokinetic Properties
Absorption:
Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to the acid form to become biologically active. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.
Distribution:
The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost can be measured in aqueous humor during the first four hours, and in plasma only during the first hour after local administration.
Metabolism:
Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid ß-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 ß-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 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.

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 unanesthetized 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 mcg/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 mcg/eye/day). In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris. Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys.
The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris with no proliferative changes observed. The change in iris colour may be permanent.
In chronic ocular toxicity studies, administration of latanoprost 6 mcg/eye/day has also been shown to induce increased palpebral fissure. This effect is reversible and occurs at doses above the clinical dose level. The effect has not been seen in humans.
Carcinogenesis:
Carcinogenicity studies in mice and rats were negative.
Mutagenesis:
Latanoprost was found negative in reverse mutation tests in bacteria, gene mutation in mouse lymphoma and mouse micronucleus test. Chromosome aberrations were observed *in vitro* with human lymphocytes. Similar effects were observed with prostaglandin $F_{2\alpha}$, a naturally occurring prostaglandin, and indicates that this is a class effect.
Additional mutagenicity studies on *in vitro*/*in vivo* unscheduled DNA synthesis in rats were negative and indicate that latanoprost does not have mutagenic potency.
Impairment of Fertility:
Latanoprost has not been found to have any effect on male or female fertility in animal studies. In the embryotoxicity study in rats, no embryotoxicity was observed at intravenous doses (5, 50 and 250 mcg/kg/day) of latanoprost. However, latanoprost induced embryolethal effects in rabbits at doses of 5 mcg/kg/day and above. Latanoprost has been shown to cause embryofetal toxicity in rabbits characterized 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 (0.2 mg/ml), Sodium dihydrogen phosphate monohydrate, Disodium phosphate anhydrous, Water for injection.

6.2 Incompatibilities
In vitro studies have shown the precipitation occurs when eye drops containing thiomersal are mixed with latanoprost.
If such medicinal products are used the eye drops shall be administered with an interval of at least five minutes.

6.3 Shelf Life
Shelf life: 3 years.
Shelf life after opening container: 1 month.

6.4 Special Precautions for Storage
Store unopened bottle(s) under refrigeration at 2°C to 8°C (36°F to 46°F).
Once a bottle is opened for use, it may be stored at room temperature up to 25°C (77°F) for 1 month.
Protect from light.

6.5 Nature and Contents of Container
Bottle (5 ml), dropper applicator (dropper tip), screw cap, tamper evident overcap of polyethylene.
Each bottle contains 2.5 ml eye drop solution corresponding to approximately 80 drops of solution.

6.6 Special precautions for disposal and other handling
The tamper evident overcap should be removed before use.

7.0 DETAILS OF MANUFACTURER
Pfizer Manufacturing Belgium NV
Rijksweg 12, 2870
Puurs- Belgium

Imported and Marketed in India by:
Mylan Pharmaceuticals Private Limited
BLD No. 16, Room No. 1&2,
Survey No. 99/1, Village Nimji, Kalameshwar - 441501, Nagpur, Maharashtra, India.

8.0 DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE
IL/FF-000647-RC/FF-002306 Dated 02 May 2023 (The license is renewed every 3 years per regulations).

9.0. DATE OF REVISION
May 2023
For reporting of adverse events and PV related queries please write on
Email: ProductSafety@viatris.com

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PAA206348

Process Black

VIATRIS					
Description	Xalatan_0.05mg_ml_Bottle_2.5ml			Date: 29 May 23	Time: 21:00
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Packing Site/Printer	Pfizer Manufacturing Puurs (Puurs - BE)	Keyline/Drawing No.	I028_05/F		
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Supplier SAP No.	N/A	Source code	0058		
Sign-offs					
					V2 Oct 2022