

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE MEDICINAL PRODUCT**

Xalatan 0.005 % w/v eye drops solution.

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

100 ml eye drops solution contains 0.005 g latanoprost.

One drop contains approximately 1.5 micrograms latanoprost.

Excipient: Benzalkonium chloride 0.02 % w/v is included as a preservative.

For a 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, 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**

##### **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 precautions for use**

#### **Iris pigmentation changes**

Latanoprost may gradually increase the brown pigment of the iris. The eye colour 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 colour 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-coloured irides that contain the colour 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 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 treatment of inflammatory neovascular glaucoma. Therefore, it is recommended that latanoprost should be used with caution in these conditions until more experience is obtained.

### **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 suffer 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 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

### 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 foetus (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**

| <b>System Organ Class</b>              | <b>Common<br/>≥ 1/100 to &lt;<br/>1/10</b> | <b>Uncommon<br/>≥ 1/1 000 to<br/>&lt; 1/100</b> | <b>Rare<br/>≥ 1/10 000<br/>to &lt; 1/1 000</b> | <b>Frequency not<br/>known<br/>(cannot be<br/>estimated<br/>from available<br/>data)</b> |
|----------------------------------------|--------------------------------------------|-------------------------------------------------|------------------------------------------------|------------------------------------------------------------------------------------------|
| <i>Infections and<br/>infestations</i> |                                            |                                                 |                                                | Herpetic<br>keratitis*                                                                   |
| <i>Nervous system<br/>disorders</i>    |                                            | Dizziness*;<br>headache*                        |                                                |                                                                                          |

|                                                             |                                                                                                                                                                                                                                                                                            |                                                                                                     |                          |                                                                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Eye disorders</i>                                        | 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* |
| <i>Cardiac disorders</i>                                    |                                                                                                                                                                                                                                                                                            | Angina; palpitations*                                                                               |                          | Angina unstable*                                                                                                                                                                                                                                                                                 |
| <i>Respiratory, thoracic and mediastinal disorders</i>      |                                                                                                                                                                                                                                                                                            | Asthma*; dyspnoea*                                                                                  |                          | Asthma aggravation*; acute asthma attacks*                                                                                                                                                                                                                                                       |
| <i>Gastrointestinal disorders</i>                           |                                                                                                                                                                                                                                                                                            | Nausea*                                                                                             | Vomiting*                |                                                                                                                                                                                                                                                                                                  |
| <i>Skin and subcutaneous tissue disorders</i>               |                                                                                                                                                                                                                                                                                            | Rash                                                                                                | Pruritus                 |                                                                                                                                                                                                                                                                                                  |
| <i>Musculoskeletal and connective tissue disorders</i>      |                                                                                                                                                                                                                                                                                            | Myalgia*; arthralgia*                                                                               |                          |                                                                                                                                                                                                                                                                                                  |
| <i>General disorders and administration site conditions</i> |                                                                                                                                                                                                                                                                                            | 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 ( $\square$  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 shortterm 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).

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after marketing 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 according to their local requirements.

## **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 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).

## **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.

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 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.

### **Vision preserving effects**

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 analysed 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;  $p=0.0003$ ).

This trial has demonstrated the vision-preserving benefits with an IOP lowering drug latanoprost in patients with mild to moderate open angle glaucoma.

### **Paediatric population**

The efficacy of Xalatan in paediatric patients  $\leq 18$  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<br>N=53 |                 | Timolol<br>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<br>N=28         | Non-PCG<br>N=25 | PCG<br>N=26     | Non-PCG<br>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  $\geq 1$  month); 1 patient in nonlatanoprost prostaglandin analogues (PGA) group (continuously treated with non-latanoprost PGA for  $\geq 1$  month); and 38 in PGA unexposed (not treated continuously with any PGA for  $\geq 1$  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 rate 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  $0.16 \pm 0.02$  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 metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid  $\omega$ -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  $\omega$ -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 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 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<sub>2α</sub>, 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 micrograms/kg/day) of latanoprost. However, latanoprost induced embryoletal effects in rabbits at doses of 5 micrograms/kg/day and above. Latanoprost has been shown to cause embryofoetal toxicity in rabbits characterized by increased incidences of late resorption and abortion and reduced foetal 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 (E339i)

Disodium hydrogen phosphate anhydrous (E339ii)

Water for injection

### **6.2. Incompatibilities**

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

### **6.3. Shelf life**

Do not use XALATAN after the expiry date which is stated on the Carton/Bottle label after EXP:.. The expiry date refers to the last day of that month.

#### **6.4. Special precautions for storage**

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

Once opened the container may be stored at room temperature below 25 °C.

To be used within 4 weeks after opening.

#### **6.5. Nature and contents of container**

Dropper container (5 ml) of polyethylene with either a screw cap and tamper evident overcap of polyethylene or with a screw cap and tamper-evident ring.

Each dropper container contains 2.5 ml eye drops solution corresponding to approximately 80 drops of solution.

Pack size: 1 x 2.5 ml.

#### **6.6. Instructions for use and handling**

Keep out of the sight and reach of children.

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

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

#### **7. FURTHER INFORMATIONMANUFACTURED BY:**

Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs, Belgium

#### **8. PRESCRIPTION STATUS**

Prescription only medicine

#### **9. DATE OF REVISION OF THE TEXT**

July 2025