# XALATAN™

## 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

**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).

**Pediatric population**

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

## 4.3 Contraindications

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 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.

The potential for heterochromia exists for patients receiving unilateral treatment.

**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 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.

**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**

Latanoprost 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 (4 patients) are very limited (see section 5.1). No data are available for pre-term 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.

Long-term safety in children has not yet been established.

**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: ADRs by SOC and CIOMS frequency category (i.e., Very common, Common, Uncommon, Rare, and Very rare) and in order of decreasing medical seriousness within each frequency category and SOC.

| **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; | 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 |

| **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)** |
|---|---|---|---|---|
| | blepharitis; conjunctivitis* | | | 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 eye drops 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.

### 4.9 Overdose

If overdosage with latanoprost occurs, treatment should be symptomatic.

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 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 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.

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.

**Paediatric population**

The efficacy of latanoprost 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 pre-term 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[t] (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[t] (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.

[t] Adjusted estimate based on 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 $\pm$ 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 $\beta$-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 $\beta$-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 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 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 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 embryolethal effects in rabbits at doses of 5 micrograms/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, sodium dihydrogen phosphate monohydrate, disodium phosphate anhydrous, and water for injection.

### 6.2 Shelf Life

Shelf-life: 3 years.

Shelf-life after opening container: 6 weeks.

### 6.3 Special Precautions for Storage

Store unopened bottle under refrigeration at 2°C to 8°C.

When a bottle is opened for use, it may be stored at room temperature up to 30°C for 6 weeks.

Protect from light.

## 7. MARKETING AUTHORISATION HOLDER

Viatris (Thailand) Limited

PI Revision No.: 7.1

PI date: October 17, 2024

Country: Thailand