

## TANUP

## Eye Drops

### Composition

Latanoprost 0.05mg/ml

### Action

Latanoprost is a prostanoid selective FP receptor agonist that is believed to reduce the intraocular pressure (IOP) by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

#### Pharmacodynamics

Reduction of the IOP in man starts about 3-4 hours after administration and maximum effect is reached after 8-12 hours. IOP reduction is present for at least 24 hours.

### Pharmacokinetics

#### Absorption

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

#### 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 4 hours, and in plasma only during the first hour after local administration. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical 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 are recovered in the urine after topical and intravenous dosing, respectively.

### Indications

TANUP (latanoprost) is indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. TANUP may be used for the reduction of intraocular pressure in patients with chronic angle-closure glaucoma who underwent peripheral iridotomy or laser iridoplasty.

### Contraindications

Known hypersensitivity to latanoprost, or any other ingredients in this product.

### Warnings & Precautions

#### General

Latanoprost has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes, and growth of eyelashes. Pigmentation is expected to increase as long as LATANOPROST is administered. After discontinuation of LATANOPROST, pigmentation of the iris is likely to be permanent while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in

some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The effects of increased pigmentation beyond 5 years are not known. Patients who are expected to receive treatment in only one eye should be informed about the potential for increased pigmentation in the treatment eye and thus, heterochromia between the eyes.

LATANOPROST may gradually increase the pigmentation of the iris. This effect has predominantly been seen in patients with mixed coloured irides, i.e., blue-brown, grey-brown, green-brown or yellow-brown. The eye colour change is due to increased melanin content in the stromal melanocytes rather than to an increase in the number of melanocytes. This change may not be noticeable for several months to years. 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. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with LATANOPROST can be continued in patients who develop noticeably increased pigmentation, these patients should be examined regularly.

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.

#### **Hepatic/Biliary/Pancreatic**

LATANOPROST has not been studied in patients with hepatic impairment and should, therefore, be used with caution in such patients.

#### **Ophthalmologic**

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. LATANOPROST should be used with caution in patients who do not have an intact posterior capsule or who have known risk factors for macular edema.

There is no experience with LATANOPROST in patients with inflammatory ocular conditions, inflammatory glaucoma, neovascular glaucoma or congenital glaucoma, and only limited experience with pseudophakic patients and in patients with pigmentary glaucoma .

LATANOPROST should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Latanoprost should be used with caution in patients with a history of herpetic keratitis. Latanoprost 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.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of ocular epithelial surface.

This product contains benzalkonium chloride as a preservative, which may be absorbed by soft contact lenses. Remove contact lenses before administration of Latanoprost. Contact lenses may be reinstalled 15 minutes after administering Latanoprost.

#### **Renal**

LATANOPROST has not been studied in patients with renal impairment and should, therefore, be used with caution in such patients.

#### **Respiratory**

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

#### **Sexual Function/Reproduction**

**Fertility:** Latanoprost has not been found to have any effect on male or female fertility in animal studies.

### **Skin**

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, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment .

### **Special Populations**

**Pregnant Women:** Reproduction studies have been performed in rats and rabbits. In rabbits an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. LATANOPROST should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Women:** The active substance in LATANOPROST and its metabolites may pass into breast milk and LATANOPROST should therefore be used with caution in nursing women.

**Pediatrics:** The safety and efficacy of the use of LATANOPROST in children has not been established.

### **Adverse Reactions**

#### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The ocular adverse events and ocular signs and symptoms reported in 5 to 15% of the patients on latanoprost)in the three 6 month, multi-centre, double-masked, active-controlled trials were blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased iris pigmentation and punctate epithelial keratopathy.

Local conjunctival hyperemia was observed: however, less than 1% of the LATANOPROST treated patients required discontinuation of therapy because of intolerance to conjunctival hyperemia.

In addition to the above listed ocular events/signs and symptoms, the following were reported in 1to 4% of the patients: dry eye, excessive tearing, eye pain, lid crusting, lid edema, lid erythema, lid discomfort/pain and photophobia.

The most common systemic adverse events seen with LATANOPROST were upper respiratory tract infection/cold/ u which occurred at a rate of approximately 4%. Pain in muscle/joint/back, chest pain/angina pectoris and rash/allergic skin reaction each occurred at a rate of 1 to 2% .

#### **Less Common Clinical Trial Adverse Drug Reactions (<1%)**

The following events were reported in less than 1% of the patients: conjunctivitis, diplopia and discharge from the eye.

During clinical studies, there were extremely rare reports of the following: retinal artery embolus, retinal detachment, and vitreous hemorrhage from diabetic retinopathy.

#### **Post-Market Adverse Drug Reactions**

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 a torn posterior lens capsule, or in patients with known risk factors for macular edema. LATANOPROST should be used with caution in these patients. Upon discontinuation of LATANOPROST treatment, visual acuity has improved, in some cases with concurrent treatment with topical steroidal and non-steroidal anti-inflammatory drugs.

LATANOPROST has been reported to cause darkening, thickening and lengthening of eye lashes. Based on spontaneous reports, rare cases of iritis/uveitis and very rare cases of darkening of the palpebral skin have been reported.

The following events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to LATANOPROST, or a combination of these factors, have been reported during postmarketing use of LATANOPROST in clinical practice and in the literature: eyelash changes (increased length, thickness, pigmentation of eyelashes, increased number of eyelashes and vellus hairs on the eyelid, curling of eyelashes, misdirected eyelashes sometimes resulting in eye irritation); eyelid skin darkening: periorbital and lid changes resulting in deepening of the eyelid sulcus; intraocular inflammation (iritis/uveitis); macular edema, including cystoid macular edema; corneal edema and erosions; localized skin reaction on the eyelid; photophobia; toxic epidermal necrolysis; infections and infestations: herpetic keratitis. Those events are reported voluntarily from a population of unknown size; therefore, estimates of frequency cannot be made. Rare cases of asthma, asthma aggravation, acute asthma attack and dyspnoea have been reported. There is limited experience from patients with asthma but latanoprost neither was found to affect pulmonary function when studied in a small number of steroid treated patients suffering from moderate asthma nor was it found to affect the pulmonary function, airway reactivity or  $\beta$ 2-responsiveness when studied in a small number of non-steroid treated asthma patients.

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.

## **Drug Interactions**

*In vitro* studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with LATANOPROST. If such drugs are used, they should be administered with an interval of at least 5 minutes between applications.

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.

## **Dosage and Administration**

### **Dosing Considerations**

Optimal effect is obtained if TANUP (latanoprost) is administered in the evening.

### **Recommended Dose and Dosage Adjustment**

The recommended dose for adults, including the elderly (over 60 years of age), is one drop in the affected eye(s) once daily.

The dose of TANUP should not exceed once daily as it has been shown that more frequent administration decreases the IOP lowering effect. Reduction of IOP in humans starts about 3 to 4 hours after treatment and maximum effect is reached after 8 to 12 hours. Pressure reduction is maintained for at least 24 hours.

### **Missed Dose**

If one dose is missed, treatment should continue with the next dose the following day.

### **Administration**

Contact lenses should be removed prior to the administration of TANUP, and may be reinserted 15 minutes after administration.

*Use in combination with other drugs*

TANUP may be used concomitantly with other topical ophthalmic products to further lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

**Over Dosage**

Apart from ocular irritation and conjunctival or episcleral hyperemia, no other ocular side effects of latanoprost administered at high doses are known. Intravenous infusion of up to 3 µg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and no adverse reactions were observed. Intravenous doses of 5.5 to 10 µg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea and sweating.

In monkeys, latanoprost has been infused i.v. in doses of up to 500 µg/kg without major effects on the cardiovascular system. Intravenous administration in monkeys has been associated with transient bronchoconstriction. However, in patients with bronchial asthma, bronchoconstriction was not induced by latanoprost when administered topically to the eyes at a dose 7 times the recommended clinical dose. If overdosage with latanoprost occurs, treatment should be symptomatic.

**Presentation**

**Tanup Eye Drops**

Bottle of 2.5 ml