SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

Latanoprost Ophthalmic Solution 0.005% w/v.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Latanoprost ……..…..0.05 mg
Benzalkonium Chloride (50%) ……..... 0.4 mg.
(As preservative)
Water for Injection..…….. q.s.

3. PHARMACEUTICAL FORM

Ophthalmic solution.

Description
A clear, colourless solution, practically free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension in adults (including the elderly).
- Reduction of elevated IOP in paediatric patients with elevated IOP and paediatric glaucoma.

4.2 Posology and Method of Administration

For topical ocular instillation.

Adults (including the elderly)
Recommended dosage is one drop in the affected eye(s) once daily. Optimal effect is obtained if solution is administered in the evening.
The dosage 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.
Or, as directed by the Physician.

Paediatric Population
Same dosage is recommended as like adults. Data is not available for use in preterm infants (gestational age < 36 weeks). Further, data in the age group < 1 year is limited.

Method of Administration

- For ocular (external) use only.
- As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac is compressed at the medial canthus (punctal occlusion) for one minute. This should be performed immediately following the instillation of each drop.
- Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.

- If more than one topical ophthalmic medicinal product is being used, the medicinal products should be instilled 5 to 15 minutes apart. Eye ointments should be administered last.
- Patients should be instructed to avoid contact between the dropper tip and the eye or eyelids.
- After the first opening the bottle do not store above 25°C and use within four weeks.

4.3 Contraindications

Latanoprost Eye Drops are contraindicated in patient with known hypersensitivity to the latanoprost or to any of the excipients listed in section 6.1.

4.4 Special Warnings and Precautions for Use

Treatment with this product may gradually change eye colour by increasing the amount of brown pigment in the iris. Before treatment is instituted, patients should be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia.

This change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e., blue-brown, grey-brown, yellow-brown and green-brown. Clinical studies of latanoprost showed that the onset of this change is usually within the first 8 months of treatment, rarely during the second or third year, and has not been seen after the fourth year of treatment. The rate of progression of iris pigmentation decreases with time and is stable for 5 years. The effect of increased pigmentation beyond 5 years has not been evaluated. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation. The iris colour change is slight in the majority of cases and often not observed clinically. The incidence in patients with mixed colour irides ranged from 7 to 85%, with yellow-brown irides having the highest incidence. In patients with homogeneously blue eyes, no change has been observed and in patients with homogeneously grey, green or brown eyes, the change has only rarely been seen.

The colour change is due to increased melanin content in the stromal melanocytes of the iris and not to an increase in number of melanocytes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. No further increase in brown iris pigment has been observed after discontinuation of treatment. It has not been associated with any symptom or pathological changes in clinical trials to date.

Neither naevi nor freckles of the iris have been affected by treatment. Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical trials. Based on 5 years clinical experience, increased iris pigmentation has not been shown to have any negative clinical sequelae and latanoprost can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, latanoprost treatment may be discontinued.

There is limited experience of latanoprost in chronic angle closure glaucoma, open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. There is no experience of latanoprost in inflammatory and neovascular glaucoma or inflammatory ocular conditions. Latanoprost eye drops have no or little effect on the pupil, but there is no experience in acute attacks of closed angle glaucoma. Therefore, it is recommended that latanoprost should be used with caution in these conditions until more experience is obtained.

There are limited study data on the use of latanoprost during the peri-operative period of cataract surgery. Latanoprost should be used with caution in these patients.

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.

Reports of macular oedema have occurred mainly in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema (such as diabetic retinopathy and retinal vein occlusion). Latanoprost should be used with caution in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.
In patients with known predisposing risk factors for iritis/uveitis, latanoprost 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.
Periorbital skin discolouration has been observed, the majority of reports being in Japanese patients. Experience to date shows that periorbital skin discolouration is not permanent and in some cases has reversed while continuing treatment with latanoprost.
Latanoprost may gradually change eyelashes and vellus hair in the treated eye and surrounding areas; these changes include increased length, thickness, pigmentation, number of lashes or hairs and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.

Preservative - Benzalkonium Chloride (BKC)
Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.
From the limited data available, there is no difference in the adverse event profile in children compared to adults. However, eyes in children generally show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children.

Contact Lenses
Contact lenses may absorb benzalkonium chloride and these should be removed before instilling this eye drops but may be reinserted after 15 minutes.
Paediatric Population
Efficacy and safety data in the age group < 1 year (4 patients) are very limited. No data are available for preterm infants having gestational age < 36 weeks.
In children from 0 to < 3 years old that mainly suffer from primary congenital glaucoma (PCG), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment.
Long-term safety in children has not yet been established.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction
Definitive drug interaction data are not available. There have been reports of paradoxical elevations in IOP following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended.

4.6 Fertility, Pregnancy and Lactation

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

Breast Feeding
Latanoprost and its metabolites may pass into breast milk. Therefore, this product should not be used in breast-feeding women or if therapy is essential to mother, breastfeeding should be temporary discontinued.

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

4.7 Effects on Ability to Drive and Use Machines
Latanoprost Eye Drops have minor influence on the ability to drive and use machines. In common with other eye preparations, instillation of eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines.

4.8 Undesirable Effects
The majority of adverse reactions relate to the ocular system. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation. 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	Common	Uncommon	Rare	Very Rare
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; blepharitis; eye pain; photophobia; conjunctivitis	Eyelid oedema; dry eye; keratitis; blurred vision; macular oedema including cystoid macular oedema; uveitis	Iritis; corneal oedema; corneal erosion; periorbital oedema; trichiasis; distichiasis; iris cyst; localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids; pseudopemphigoid of ocular conjunctiva	Periorbital and lid changes resulting in deepening of the eyelid sulcus
Cardiac disorders			Angina; palpitations		Angina unstable

Respiratory, thoracic and mediastinal disorders			Asthma; dyspnoea	Asthma exacerbation	
Gastrointestinal disorders			Nausea; vomiting		
Skin and subcutaneous tissue disorders			Rash	Pruritus	
Musculoskeletal and connective tissue disorders			Myalgia; arthralgia		
General disorders and administration site conditions			Chest pain		

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. Adverse events seen more frequently in the paediatric population as compared to adults are nasopharyngitis and pyrexia.

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

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4.9 Overdose

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

Treatment
If latanoprost is accidentally ingested the following information may be useful. More than 90% is metabolised 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 to 10 mcg/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes, and sweating. In monkeys, latanoprost has been infused intravenously

in doses of up to 500 mcg/kg without major effects on the cardiovascular system. Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost.
If overdosage with latanoprost occurs, treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group: Ophthalmologicals; Antiglaucoma preparations and miotics, prostaglandin analogues.
ATC Code: S01EE01.

Mechanism of Action

Latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a selective prostanoid FP receptor agonist which reduces the intraocular pressure (IOP) by increasing the outflow of aqueous humour. Studies in animals and human 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 human.

Pharmacodynamic Effects

Reduction of the IOP in human starts about 3 to 4 hours after administration of latanoprost eye drops and maximum effect is reached after 8 to 12 hours. Pressure reduction is maintained for at least 24 hours.
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.

Clinical Efficacy and Safety

Pivotal studies have demonstrated that latanoprost 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).
Patients with mean baseline intraocular pressure of 24 to 25 mmHg who were treated for 6 months in multi-center, randomized, controlled trials demonstrated 6 to 8 mmHg reductions in intraocular pressure. This IOP reduction with Latanoprost Ophthalmic Solution 0.005% dosed once daily was equivalent to the effect of timolol 0.5% dosed twice daily.
A 3-year open-label, prospective safety study with a 2-year extension phase was conducted to evaluate the progression of increased iris pigmentation with continuous use of Latanoprost once daily as adjunctive therapy in 519 patients with open-angle glaucoma. The analysis was based on observed-cases population of the 380 patients who continued in the extension phase. Results showed that the onset of noticeable increased iris pigmentation occurred within the first year of treatment for the

majority of the patients who developed noticeable increased iris pigmentation. Patients continued to show signs of increasing iris pigmentation throughout the 5 years of the study. Observation of increased iris pigmentation did not affect the incidence, nature, or severity of adverse events (other than increased iris pigmentation) recorded in the study. IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

5.2 Pharmacokinetic Properties

Absorption
Latanoprost is an isopropyl ester prodrug which is inactive as such, but, after hydrolysis to the acid of latanoprost becomes biologically active.
The prodrug is well absorbed through the cornea and all drug that enters the aqueous humour is hydrolysed during the passage through the cornea.

Distribution
Human studies indicate that the peak concentration in the aqueous humour is reached about 2 hours after topical administration. After topical application in monkeys, latanoprost is distributed primarily in the anterior segment, the conjunctivae and the eyelids. Only minute quantities of the drug reach the posterior segment.

Biotransformation
There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver.

Elimination
The half-life in plasma is 17 minutes. The main metabolites, the 1,2-dinor and 1,2,3,4-tetranor metabolites, exert no or only weak biological activity in animal studies and are excreted primarily in the urine.

Paediatric Population
An open-label pharmacokinetic study of plasma latanoprost acid concentrations was undertaken in 22 adults and 25 paediatric patients (birth to < 18 years of age) with ocular hypertension and glaucoma. All age groups were treated with latanoprost 50 mcg/ml, one drop daily in each eye for a minimum of 2 weeks. Latanoprost acid systemic exposure was approximately 2-fold higher in 3 to < 12 year olds and 6-fold higher in children < 3 years old compared with adults, but a wide safety margin for systemic adverse effects was maintained. 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
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
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 unanaesthetised monkeys have been shown to increase the respiration rate probably reflecting bronchoconstriction of short duration. In animal studies, latanoprost has not been found to have sensitising properties.
In the eye, no toxic effects have been detected with doses of up to 100 micrograms/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 mcg/eye/day). In monkeys, however, latanoprost has been shown to induce increased pigmentation of the iris.
The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris with no proliferative changes observed. The change in iris colour may be permanent.
In chronic ocular toxicity studies, administration of latanoprost 6 micrograms/eye/day has also been shown to induce increased palpebral fissure. This effect is reversible and occurs at doses above the clinical dose level. The effect has not been seen in humans.

Carcinogenesis, Mutagenesis, Impairment of Fertility, Teratogenicity
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 F2α, a naturally occurring prostaglandin, and indicate 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. Carcinogenicity studies in mice and rats were negative.
Latanoprost has not been found to have any effect on male or female fertility in animal studies. In the embryotoxicity study in rats, no embryotoxicity was observed at intravenous doses (5, 50 and 250 micrograms/kg/day) of latanoprost. However, latanoprost induced embryolethal effects in rabbits at doses of 5 mcg/kg/day and above.
The dose of 5 mcg/kg/day (approximately 100 times the clinical dose) caused significant embryofoetal toxicity characterised by increased incidence of late resorption and abortion and by reduced foetal weight. No teratogenic potential has been detected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Benzalkonium Chloride, Monobasic Sodium Phosphate (Monohydrate), Dibasic Sodium Phosphate, Sodium Chloride, Water for Injection.

6.2 Incompatibilities
Not known.

6.3 Shelf-life
24 months

6.4 Special Precautions for Storage
Store between 2°C and 8°C.
Keep the bottle in the outer carton to protect from light.

6.5 Nature and Contents of Container

2.5 ml solution in 5 ml LDPE vials with an insert cap assembly.

6.6 Special Precautions for Disposal and Other Handling

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

06754/08218/REN/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Nov 04, 2021

10. DATE OF REVISION OF THE TEXT

August 2023