SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Latanoprost 0.005% w/v eye drops solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml eye drops solution contains 50 micrograms latanoprost.
One drop contains approximately 1.5 micrograms latanoprost.

Excipients with known effect:
Benzalkonium chloride 0.20 mg/ml, sodium dihydrogen phosphate monohydrate 4.60 mg/ml and anhydrous disodium phosphate 4.74 mg/ml (phosphate buffers).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.
Colourless, odourless solution, practically clear and practically free from particles.
pH 6.5 – 6.9
Osmolality 250 – 320 mOsm/kg

4.1 Therapeutic indications

Reduction of elevated intraocular pressure (IOP)

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

4.2 Posology and method of administration

Posology

Adults (including the elderly)

Recommended therapy is one eye drop in the affected eye(s) once daily. Optimal effect is obtained if latanoprost eye drops is administered in the evening.

The dosage of latanoprost eye drops 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.

Paediatric population
Latanoprost 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).

Method of administration
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 administered at least five minutes apart.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Latanoprost eye drops 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 irises, i.e. blue-brown, grey-brown, yellow-brown and green-brown. In studies with latanoprost, the onset of the 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 five years. The effect of increased pigmentation beyond five years has not been evaluated. In an open 5-year latanoprost safety study, 33% of patients developed iris pigmentation (see section 4.8). The iris colour change is slight in the majority of cases and often not observed clinically. The incidence in patients with mixed colour irises ranged from 7 to 85%, with yellow-brown irises 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 eye drops can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, latanoprost eye drops 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 has 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 eye drops 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 eye drops should be used with caution in these patients.

Latanoprost eye drops 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 (see section 4.8) 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 eye drops 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 eye drops 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.

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.

Use of contact lenses
Latanoprost eye drops contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. Contact lenses should be removed before using this medicine and may be reinserted after 15 minutes (see section 4.2).

Benzalkonium chloride
From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children. 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.
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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 preterm infants (less than 36 weeks gestational age).

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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of this medicinal 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 eye drops should not be used during pregnancy.

Breast-feeding

Latanoprost and its metabolites may pass into breast milk and Latanoprost eye drops should therefore not be used in breast-feeding women or breast feeding should be stopped.

Fertility
Latanoprost has not been found to have any effect on male or female fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Latanoprost eye drops has 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

Summary of the safety profile
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). Other ocular adverse reactions are generally transient and occur on dose administration.

Tabulated list of adverse reactions
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	Frequency	Adverse reaction
Infections and infestations	Rare	Herpetic keratitis[1,2].
Nervous system disorders	Uncommon	Headache[1]; dizziness[1].
Eye disorders	Very common	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).
	Common	Punctate keratitis, mostly without symptoms; blepharitis; eye pain; photophobia; conjunctivitis[1].
	Uncommon	Eyelid oedema; dry eye; keratitis[1]; vision blurred; macular oedema including cystoid macular oedema[1]; uveitis[1].

	Rare	Iritis[1]; corneal oedema[1]; corneal erosion; periorbital oedema; trichiasis[1]; distichiasis; iris cyst[1,2]; localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids; pseudopemphigoid of ocular conjunctiva[1,2].
	Very rare	Periorbital and lid changes resulting in deepening of the eyelid sulcus.
Cardiac disorders	Uncommon	Angina; palpitations[1].
	Very rare	Angina unstable.
Respiratory, thoracic and mediastinal disorders	Uncommon	Asthma[1]; dyspnoea[1].
	Rare	Asthma exacerbation.
Gastrointestinal disorders	Uncommon	Nausea, vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash.
	Rare	Pruritus.
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia[1]; arthralgia[1].
General disorders and administration site conditions	Uncommon	Chest pain[1].

[1] ADR identified post-marketing.

[2] ADR frequency estimated using "The rule of 3".

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.

Description of selected adverse reactions

No information is provided.

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.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Treatment
If latanoprost eye drops are accidentally ingested the following information may be useful: One bottle contains 125 micrograms latanoprost. More than 90% is metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers induced no symptoms, but a dose of 5.5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. In monkeys, latanoprost has been infused intravenously in doses of up to 500 micrograms/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 eye drops occurs, treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ophthalmologicals, antiglaucoma preparations and miotics, prostaglandin analogues.
ATC code: S01EE01

The active substance latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a selective prostanoid FP receptor agonist which reduces the IOP by increasing the outflow of aqueous humour. Reduction of the IOP 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 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).

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 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 50 µg/ml 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 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 (see table) and was maintained throughout the 12 week period of study, as in adults.

Table: IOP reduction (mm Hg) 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 (MW 432.58) is an isopropyl ester prodrug which per se is inactive, 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
Studies in man indicate that the peak concentration in the aqueous humour is reached about two 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 and elimination
There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. The half-life in plasma is 17 minutes in man. 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 (from birth to < 18 years of age) with ocular hypertension and glaucoma. All age groups were treated with latanoprost 50 µg/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 (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

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 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 micrograms/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.

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. 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 micrograms/kg/day and above.

The dose of 5 micrograms/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

Sodium chloride

Benzalkonium chloride

Sodium dihydrogen phosphate monohydrate

Anhydrous disodium phosphate

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Shelf life: 36 months

Shelf life after opening of container: 4 weeks

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Keep the bottle in the outer carton in order to protect from light.

After first opening the bottle: do not store above 25°C and use within four weeks.

6.5 Nature and contents of container

Dropper container (5 ml) of polyethylene, screw cap, tamper evident overcap of polyethylene.

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

Pack sizes: 1 x 2.5 ml, 3 x 2.5 ml and 6 x 2.5ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Zentiva Pharma UK Limited
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London
EC4A 1JP
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8 MARKETING AUTHORISATION NUMBER(S)

PL 17780/0529

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