SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Latanoprost 50 micrograms/ml eye drops, solution in a single-dose container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 50 micrograms of latanoprost.

One drop contains approximately 1.5 micrograms of latanoprost.

Excipient(s) with known effect:

Sodium dihydrogen phosphate dihydrate (E339) 8.3 mg/ml.

Disodium phosphate dodecahydrate (E339) 4.8 mg/ml.

This medicine contains 6.3 mg/mL phosphates which corresponds to approximately 0.24 mg/drop.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution in a single-dose container (eye drops). Clear to light-yellow solution.

pH: 5.5 to 6.5

Osmolality: 270 to 330 mOsm/kg

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).

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 this medicine is administered in the evening.

The dosage of this medicine 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

No data available with formulation of this medicine.

Method of administration

Ocular use.

As with any eye drops, to reduce possible systemic absorption, it is recommended that the lachrymal sac be 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.

A single-dose contains enough eye drops solution to treat both eyes.

For single use only.

This medicinal product is a sterile solution that does not contain a preservative. The solution from one individual single dose container is to be used immediately after opening for administration to the affected eye(s). Since sterility cannot be maintained after the individual single dose container is opened, any remaining contents must be discarded immediately after administration.

Patients should be instructed:

- to avoid contact between the dropper tip and the eye or eyelids,

- to use the eye drops solution immediately after first opening the single-dose container and to discard the single-dose after use.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

This medicine 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. 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 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 this medicine can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, this medicine treatment may be discontinued.

There is limited experience of this medicine in chronic angle closure glaucoma, open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. There is no experience of this medicine in inflammatory and neovascular glaucoma or inflammatory ocular conditions. This medicine 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 this medicine should be used with caution in these conditions until more experience is obtained.

There is limited study data on the use of this medicine during the peri-operative period of cataract surgery. This medicine should be used with caution in these patients.

This medicine 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). This medicine 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, this medicine 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 this medicine.

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.

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 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, this medicine should not be used during pregnancy.

Breast-feeding

Latanoprost and its metabolites may pass into breast milk and this medicine 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

This medicine 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

a) 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.

b) 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	**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**	**Very Rare** <**1/10,000**
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, mostly without symptoms; blepharitis; eye pain; photophobia; conjunctivitis*	Eyelid oedema; dry eye; keratitis*; vision blurred; 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*		

*ADR identified post-marketing

§ADR frequency estimated using "The Rule of 3"

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.

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. Website: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 this medicine is overdosed.

Treatment

If this medicine is accidentally ingested the following information may be useful: One single-dose container contains 10 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 this medicine.

If overdose with this medicine occurs, treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; Antiglaucoma preparations and miotics, prostaglandin analogues.

ATC code: S01 EE01

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 this medicine 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.

Clinical efficacy and safety

Latanoprost was evaluated in a non-inferiority, randomized, investigator-masked, two-parallel group, phase III clinical trial, to evaluate the efficacy and safety of a preservative free (PF) formulation of latanoprost versus a preserved reference medicinal product in 130 patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT). The primary efficacy variable was the change in intraocular pressure (IOP) after 12 Weeks of treatment.The IOP reduction (-7.67 ± 2.104 mmHg) of latanoprost was similar to the reference product one (7.77 ± 2.500). The 97.5% CI of the between-treatment group difference in the mean diurnal IOP change from Baseline to Week 12 [-0.846, $+\infty$) did not cross the non-inferiority margin set at -1.5 mmHg. Latanoprost and the reference product were assessed for conjunctival hyperemia, ocular comfort level signs, visual acuity and slit lamp

examination. Both products were well tolerated and safe, as shown by the low incidence of adverse events (AEs) and the absence of any serious AE.

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

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.

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

Carboxymethyl cellulose sodium, D-mannitol, tyloxapol, sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, hydrochloric acid, water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Before first opening: 2 years

After first opening of container: 20 days

After first opening of the single dose container: use immediately and discard the single-dose container after use.

6.4 Special precautions for storage

Keep the single-dose containers in the sachet and the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3

6.5 Nature and contents of container

Clear, single-dose low density polyethylene (LDPE) containers with a twist-off tab.

Each single-dose container contains 0.2 ml solution. Two strips of 5 single-dose containers are enclosed within an OPET/Alu/PE sachet.

Pack sizes: 30 x 0.2 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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)

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10 DATE OF REVISION OF THE TEXT

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