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 of eye drops solution contains 50 micrograms of latanoprost (0.005% w/v).
Each drop contains 1.5 micrograms latanoprost.

Excipient with known effect: Contains 0.2 mg/ml (0.02% w/v) benzalkonium chloride.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution
The solution is a clear colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension.

Reduction of intraocular pressure in children with elevated intraocular pressure and glaucoma children.

4.2 Posology and method of administration

Recommended dosage for adults (including the elderly):
Recommended therapy is one eye 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 intraocular pressure lowering effect.

If one dose is missed, treatment should continue with the next dose as normal.

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 drug is being used, the drugs should be administered at least five minutes apart.

Paediatric population:
The dosage of Latanoprost Orifarm eye drops for children is the same as in adults. There are no data available for premature infants (gestational age less than 36 weeks). Data for the group <1 year (four patients) are very limited (see section 5.1).

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 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 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, inflammatory ocular conditions, or congenital glaucoma. Latanoprost 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 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 perioperative 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 keratitis caused by herpes simplex and in patients who have had 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 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 islimited 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.
Latanoprost contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy and may cause eye irritation. Close monitoring is required with frequent or prolonged use of Latanoprost in dry eye patients, or in conditions where the cornea is compromised.

Soft contact lenses may absorb benzalkonium chloride and become discoloured. Soft contact lenses should be removed before applying Latanoprost eye drops but may be reinserted after 15 minutes (see section 4.2).

Paediatric population
Data on efficacy and safety for age group <1 year (four patients) are very limited (see section 5.1). There are no data available for premature infants (gestational age less than 36 weeks).

For children between zero and three years of age, who mainly suffers from PCG (primary congenital glaucoma) surgery (trabeculectomy/goniotomy) is first-line treatment.

Long-term safety in children has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

There have been reports of paradoxical elevations in intraocular pressure 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 were performed on adults only.

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 should not be used during pregnancy.

Breastfeeding
Latanoprost and its metabolites may pass into breast milk and Latanoprost should therefore not be used in nursing women.

Fertility
Latanoprost has not shown 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 has minor or moderate 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. Patients should avoid driving or using machines until the vision has normalized.

4.8 Undesirable effects

The majority of adverse events 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 events are generally transient and occur on dose administration.

Adverse events are categorized by frequency as follows: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1000 to <1/100); rare (≥ 1/10 0000 to <1/1 000); very rare (<1/10 000); not known (cannot be estimated from the available data).

Infections and infestations:
Not known: Herpetic keratitis

Nervous system disorders:
Not known: Headache, dizziness.

Eye disorders:
Very common: Increased iris pigmentation; mild to moderate conjunctival hyperaemia; eye irritation (burning grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes (increased length, thickness, pigmentation and number) (vast majority of reports in Japanese population).
Common: transient punctate epithelial erosions, mostly without symptoms; blepharitis; eye pain; photophobia.
Uncommon: Eyelid oedema; dry eye; keratitus; vision blurred; conjunctivitis.
Rare: Iritis/uveitis (the majority of reports in patients with concomitant predisposing factors); macular oedema; symptomatic corneal oedema and erosions; periorbital oedema; misdirected eyelashes sometimes resulting in eye irritation; extra row of cilia at the aperture of the meibomian glands (distichiasis).
Very rare: Periorbital and eyelid changes that lead to more pronounced eyelid sulcus.
Not known: Iris cyst.

Cardiac disorders:
Very rare: Unstable angina pectoris.
Not known: Palpitations.

Respiratory, thoracic and mediastinal disorders:
Rare: Asthma, asthma exacerbation and dyspnoea.

Skin and subcutaneous tissue disorders:
Uncommon: Skin rash.
Rare: Localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids.

Musculoskeletal and connective tissue disorders:
Not known: Myalgia, arthralgia.

General disorders and administration site conditions:
Very rare: Chest pain.

Very rare cases of corneal calcification have been reported with the use of eye drops containing phosphate. In some patients, this has caused significant damage to the cornea.

Paediatric population:
In two short-term clinical trials (≤ 12 weeks) including 93 pediatric patients (25 and 68, respectively) safety profile was similar to the one seen in adults, and any new side effects was revealed. Moreover, the short-term safety profiles were similar in the pediatric subpopulations (see section. 5.1). Nasopharyngitis and pyrexia occurred more frequently in children than in adults.

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 listed in Appendix V.

4.9 Overdose

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

If Latanoprost is 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 occurs, treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: Prostaglandin analogues
ATC code: S01E E01

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

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 effect of latanoprost in pediatric patients ≤ 18 years was shown in a 12-week, double-blind clinical trial in which latanoprost was compared with timolol in 107 patients diagnosed with ocular hypertension and pediatric glaucoma. For newborns the gestational age had to be at least 36 weeks. Patients received either latanoprost 50 micrograms/ml once daily or timolol 5 mg/ml (or optionally 2.5 mg/ml in patients younger than 3 years) twice a day. The primary efficacy endpoint was the average reduction in intraocular pressure (IOP) from baseline at week 12 of the study. The average reduction in IOP in the latanoprost and timolol groups were similar. In all the age groups (0 - <3 years, 3 - <12 years and 12-18 years), the mean reduction in IOP at week 12 in latanoprost group was the same as in the timolol group. However, the efficacy data for the age group 0 - <3 years was based on only 13 patients of latanoprost and no relevant effect was observed in the 4 patients in the agegroup 0- <1 year. There are no data for premature infants (gestational age below 36 weeks).

Reduction of IOP in patients in the subgroup with primary congenital/pediatric glaucoma (PCG) was similar in the latanoprost and timolol group. The non-PCG-subgroup (e.g. juvenile glaucoma and open-angle glaucoma aphakic) showed similar results as the PCG subgroup.

An effect on IOP was observed after the first week of treatment, and the effect was maintained throughout the 12-week trial period, as in adults, see table.

Table: Reduction in IOP (mmHg) at week 12 and treatment subgroups and baseline-diagnosis

	Latanoprost N=53		**Timolol N=54**	
Baseline, average (SE)	27.3 (0.75)		27.8 (0.84)	
Average change from baseline at week 12† (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, average (SE)	26.5 (0.72)	28.2 (1.37)	26.3 (0.95)	29.1 (1.33)
Average change from baseline at week 12† (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 the covariance-analyse (ANCOVA) model.

5.2 Pharmacokinetic properties

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.

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.

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
Plasma concentrations of latanoprost acid was investigated in an open-label pharmacokinetic study with 22 adult and 25 paediatric patients (newborn to <18 years) with ocular hypertension and glaucoma. All age groups were treated with 1 drop of latanoprost 50 micrograms / ml to each eye for at least 2 weeks. Systemic exposure to latanoprost-acid was approximately 2-fold higher in children aged 3 - <12 years and 6 times higher in children <3 years compared to adults, however a wide margin of safety in respect to systemic side effects were maintained (see section. 4.9). The median time to

reach maximum plasma concentration was 5 minutes after dose administration for all age groups. The median plasma half-life was short (<20 minutes) and were similar for paediatric and adult patients and did not result in any systemic accumulation of latanoprost at steady state

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 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 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, which 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 embryofetal toxicity characterised by increased incidence of late resorption and abortion and by reduced fetal weight.

No teratogenic potential has been detected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium phosphate anhydrous
Sodium dihydrogen phosphate monohydrate

Benzalkonium chloride
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 at least 5 minutes apart.

6.3 Shelf life

Shelf life: 24 months
Shelf life after first opening: 4 weeks

6.4 Special precautions for storage

Keep the bottle in the outer carton in order to protect from light.
Store in a refrigerator (2°C – 8°C).
After first opening: Do not store above 25°C and use within four weeks.

6.5 Nature and contents of container

Dropper container: 5ml white translucent LDPE container containing 2.5 ml fill volume.
Dropper applicator: White translucent LDPE dropper.
Cap: Turquoise opaque HDPE cap.

Pack sizes: 1 x 2.5 ml, 3 x 2.5 ml or 6 x 2.5 ml bottles

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

11-02-2015