SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medical Product

Product Name : Lacoma (Latanoprost Eye Drops 0.005% w/v)

Composition:

Latanoprost USP 0.005 % w/v (50mcg/ml)
Benzalkonium chloride USPNF 0.02% w/v
(As preservative)
Water for injections q.s

Pharmaceutical Dosage Form : Ophthalmic Solution (Eye drops)

2. Qualitative & Quantitative Composition:
3. Pharmaceutical Form:

Ophthalmic Solution (Eye drops)

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:

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

Paediatric population
Latanoprost Eye drops, solution 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.
Method of administration
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.

4.3 Contraindications:

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warning 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. 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 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 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
Latanoprost contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. 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.

Contact lenses
Contact lenses may absorb benzalkonium chloride and these should be removed before applying Latanoprost 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 (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 Interactions with other medicinal products and other forms of Interactions :

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 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.

Breast-feeding
Latanoprost and its metabolites may pass into breast milk and Latanoprost 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.

4.7 Effects on ability to drive and use machine:

Latanoprost 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. Other ocular adverse reactions are generally transient and occur on dose administration.

b. Tabulated list of adverse reactions

Adverse events are categorized by frequency as follows: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) 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 hyperpigmenta tion; 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; pseudopemp higoid 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
Gastrointesti nal disorders			Nausea*; Vomiting*		
Skin and subcutaneous tissue disorders				Rash Pruritus	

Musculoskel etal and connective tissue disorders Myalgia*; arthralgia*

General disorders and administratio n 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.

4.9 Overdosage:

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: 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:

Pharmacodynamic Properties:

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

ATC code: S01EE01

Mechanism of Action

The active substance latanoprost, a prostaglandin F2α 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.

Published 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.

Published 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.

5.2 Pharmacokinetics 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
Published 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.

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 F2α, 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.

6. Pharmaceutical particulars

6.1 List of Excipients:

Benzalkonium chloride, Anhydrous Disodium Hydrogen Phosphate, Sodium Chloride, Sodium Dihydrogen Phosphate Monohydrate, Water for Injection.

6.2 Incompatibilities: Not applicable.

6.3 Shelf life: 36 months

6.4 Special Precautions for storage: Store unopened bottle(s) under refrigeration at 2°C to 8°C.

6.5 Nature and contents of container:

2.5 mL solution in 5 mL LDPE Opaque vial with HDPE cap packed into a carton along with Patient Information Leaflet.
5 mL solution in 5 mL LDPE Opaque vial with HDPE cap packed into a carton along with Patient Information Leaflet.

6.6 Special precautions for disposal: Not applicable

7. Marketing Authorization Holder:

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8. Marketing Authorization Numbers: H2008/19675/757
9. Date of first registration /renewal of the registration: Apr 07, 2009
10. Date of revision of text: Aug, 2024