Summary Product Characteristics (SPC)

1. Name of the medicinal product
Loprost Eye Drops

2. Qualitative and quantitative composition Active Ingredients:
Latanoprost 0.005%
Excipients of known effects
Benzalkonium chloride 0.02mg/ml
For Full list of the excipient see section 6.1.

3. Pharmaceutical form
Sterile ophthalmic solution.

4. Clinical particulars
4.1 Therapeutic indications
Reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension.
Reduction of elevated intraocular pressure in pediatric patients with elevated intraocular pressure and pediatric glaucoma

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 Loprost is administered in the evening.
The dosage of Loprost 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:
Loprost 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).

4.3 Contraindications
Known hypersensitivity to any component in Loprost

4.4 Special warnings and precautions for use
Loprost 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 5year 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 Loprost can be continued if iris pigmentation ensues.
However, patients should be monitored regularly and if the clinical situation warrants, Loprost treatment may be discontinued. There is limited experience of Loprost in chronic angle closure glaucoma, open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. There is no experience of Loprost in inflammatory and neovascular glaucoma or inflammatory ocular conditions. Loprost 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 Loprost should be used with caution in these conditions until more experience is obtained. There are limited study data on the use of Loprost during the perioperative period of cataract surgery. Loprost should be used with caution in these patients.
Loprost 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). Loprost 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, Loprost can be used with caution.
There is limited experience from patients with asthma, but some cases of exacerbation of asthma and/or dyspnea 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 Loprost. 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.
Loprost 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, may cause eye irritation and is known to discolour soft contact lenses. Close monitoring is required with frequent or prolonged use of Loprost in dry eye patients, or in conditions where the cornea is compromised.
Contact lenses may absorb benzalkonium chloride and these should be removed before applying Loprost but may be reinserted after 15 minutes (see section 4.2).
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 PCG (primary congenital glaucoma), surgery (e.g.trabeculotomy/goniotomy) remains the first line treatment. Longterm 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 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 have only been performed in adults.

4.6 Pregnancy and lactation

Fertility:
Latanoprost has not been found to have any effect on male or female fertility in animal studies (see section 5.3).
Pregnancy
The safety of this medicinal product for use in human pregnancy has not been stablished. It has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate. Therefore, Loprost should not be used during pregnancy.

Lactation
Latanoprost and its metabolites may pass into breast milk and Loprost should therefore not be used in breastfeeding women or breast feeding should be stopped.

4.7 Effects on 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 events relate to the ocular system. In an open 5year 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.

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 (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 lid changes resulting in deepening of the eyelid sulcus.
Not known: iris cyst
-Cardiac Disorders:
Very rare: Unstable angina.
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 eye lids.
-Musculoskeletal and Connective Tissue Disorders: Not known: Myalgia; Arthralgia.
General Disorders and Administration Site Conditions: Very rare: Chest pain.

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. c.Description of selected adverse reactions

No information is provided.
d. 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.

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 pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose

Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if Loprost is overdosed.
If Loprost 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 produced mean plasma concentrations 200 times higher than during clinical treatment and induced no symptoms, but a dose of 5.510 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 Loprost.
If overdosage with Loprost occurs, treatment should be symptomatic.

5. Pharmacological properties

5.1 Pharmacodynamic properties

The active substance latanoprost, a prostaglandin F 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 Loprost 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 (1or 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.
However, mild to moderate conjunctival or episcleral hyperaemia may occur during topical treatment.
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 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. 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 1,2dinor 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

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

- Tween 80
- PEG-400
-Disodium edetate
-Glycerin
-Benzalkonium chloride
-Highly purified water

6.2 Incompatibilities

None known to date

6.3 Shelf life

Unopened: 24 months opened: 4 weeks

6.4 Special precautions for storage

-Store 2-8°C. Once opened the container may be stored at room temperature below 25°C.
-Protect from light.
-Keep out of the reach of children.
-Discard contents four weeks after opening.

6.5 Nature and contents of container

Low-density polyethylene bottles 5 ml bottles filled with 2.5 ml of product, plug made of Low-density polyethylene and cap made of and high-density polyethylene will be used as container closure system for Loprost Eye Drops.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing authorization holder

Amman Pharmaceutical Industries (API).
Jordan / Amman, Sahab, Second King Abdullah II Industrial City. Tel: +962-6-4023072 Fax: +962-6-4023072
E-mail: info@ammanpharma.com
Manufacturing address.
Amman pharmaceuticals industries company
P.o box 89 industrial city, 11512, sahab, jordan

8. Marketing authorization number(s)

H2024/CTD6762/13157

9. Date of first authorization/renewal of the authorization:

16/02/2024.

10. Date of revision of the text

24 April 2024