SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Loprostan Eye Drops

2. Qualitative and quantitative composition
Active Ingredients:
Latanoprost 0.005%
Timolol maleate 0.5%

Excipients with known effects:
Sodium.

Full list of the excipient in section 6.1.

3. Pharmaceutical form
Sterile Eye Drops

4. Clinical particulars
4.1 Therapeutic indications
Reduction of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues

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.
If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.
Paediatric population
Safety and effectiveness in children and adolescents has not been established. Method of Administration 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.
When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications
Loprostan is contraindicated in patients with:
• Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
• Sinus bradycardia, sick sinus syndrome, sino-atrial block, second- or third-degree atrioventricular block not controlled with pace-maker, overt cardiac failure, cardiogenic shock.
• Hypersensitivity to the active substances or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use
Systemic effects
Like other topically applied ophthalmic agents, Loprostan is absorbed systemically. Due to the betaadrenergic component timolol, the same types

of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemicADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Cardiac reactions, and rarely, death in association with cardiac failures

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma. Loprostan should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk. **Hypoglycemia/diabetes**

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Other beta-blocking agents

The effect on intra-ocular pressure or the known effects of systemic betablockade may be potentiated when timolol is given to the patients already receiving a systemic beta- blocking agent.

The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5).

Anaphylactic reactions

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Concomitant therapy

Timolol may interact with other drugs see section 4.5.

The use of two local beta-blockers or two local prostaglandins is not recommended. Ocular effects

Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Similar to experience with latanoprost eye drops, increased iris pigmentation in some patient treated with Loprostan. This effect has predominantly been seen in patients with mixed coloured irides, i.e. green-brown, yellow-brown or blue/grey- brown, and is due to increased melanin content in the stromal melanocytes of the iris. 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. The change in iris colour occurs slowly and may not be noticeable for several months to years and it has not been associated with any symptom or pathological changes.
No further increase in brown iris pigment has been observed after discontinuation of treatment, but the resultant colour change may be permanent.
Neither naevi nor freckles of the iris have been affected by the treatment. Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed but patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased iris pigmentation ensues. Before treatment is instituted patients should be informed of the possibility of a change in eye colour. Unilateral treatment can result in permanent heterochromia.
Latanoprost has no or little effect on the pupil.
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. Macular oedema, including cystoid macular oedema, has been occurred during treatment with latanoprost, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema. Loprostan should be used with caution in these patients.

Use of contact lenses
Loprostan contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride cause punctuate 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 Loprostan 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 Loprostan but may be reinserted after 15 minutes (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction
No specific drug interaction has been performed with Loprostan
There have been 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.
There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine. **Potentiated systemic beta blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.** The effect on intraocular pressure or the known effects of systemic betablockade may be potentiated when Loprostan is given

to patients already receiving an oral beta-adrenergic blocking agent, and the use of two or more topical beta-adrenergic blocking agents is not recommended.
Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.
The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking betablockers.
Beta-blockers may increase the hypoglycaemic effect of anti-diabetic agents.
Beta- blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4)

4.6 Pregnancy and lactation

Pregnancy

Latanoprost

The potential risk for humans is unknown.

Timolol

Timolol should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.
If Loprostan is administered until delivery, the neonate should be carefully monitored during the first days of life.
Consequently, Loprostan should not be used
during pregnancy. Breast-feeding

Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant.
To reduce the systemic absorption, see section 4.2.
Latanoprost and its metabolites may pass into breast milk. Loprostan should therefore not be used in women who are breast-feeding.

Fertility

Neither Latanoprost nor timolol have been found to have any effect on male or female fertility inanimal studies.

4.7 Effects on ability to drive and use machines

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

For latanoprost, the majority of adverse events relate to the ocular system, increased iris pigmentation, which may be permanent. Other ocular adverse events are generally transient and occur on dose administration. For timolol, the most serious adverse events are systemic in nature, including bradycardia, arrhythmia, congestive heart failure, bronchospam and allergic reactions.
Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation.
This may cause similar undesirable effects as seen with systemic beta blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.
Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

Treatment related adverse events Loprostan are listed below.
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).
Nervous system disorders
Uncommon:
Headache **Eye disorders**
Very common: Increased iris pigmentation.
Common: Eye irritation (including stinging, burning and itching), eye pain
Uncommon: Eye hyperaemia, conjunctivitis, vision blurred, lacrimation increased, blepharitis, corneal disorders Skin and subcutaneous tissue disorders
Uncommon: Skin rash, pruritus
For latanoprost, these are: Infections and infestations
Herpetic keratitis Nervous system disorders
Dizziness
Eye disorders
Eyelash and vellus hair changes (increased length, thickness, pigmentation, and number), punctate epithelial erosions, periorbital oedema, iritis/uveitis, macular oedema (in aphakic, pseudophakic patients with torn posterior lens capsules or in patients with known risk factors for macular oedema), dry eye, keratitis, corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation, iris cyst, photophobia, periorbital and lid changes resulting in deepening of the eyelid sulcus
Cardiac disorders
Aggravation of angina in patients with pre-existing disease, palpitations Respiratory, thoracic and mediastinal disorders
Asthma, asthma aggravation, dyspnoea
Skin and subcutaneous tissue disorders
Darkening of palpebral skin Musculoskeletal and connective tissue disorders Joint pain, muscle pain General disorders and administration site conditions Chest pain

For timolol, these are: Immune system disorders
Systemic allergic reactions including angioedema, urticaria, localised and generalised rash, pruritus, anaphylactic reaction Metabolism and nutrition disorders
Hypoglycaemia
Psychiatric disorders
Insomnia, depression, nightmares, memory loss Nervous system disorders
Syncope, cerebrovascular accident, cerebral ischaemia, increase in signs and symptoms of myasthenia gravis, dizziness, paresthesia, and headache
Eye disorders
Signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing and redness), blepharitis, keratitis, blurred vision and choroidal detachment following filtration surgery (see section 4.4), decreased corneal sensitivity, dry eyes, corneal erosion ptosis, diplopia Ear and labyrinth disorders
Tinnitus
Cardiac disorders: Bradycardia, chest pain, palpitations, oedema, arrhythmia, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure
Vascular disorders
Hypotension, Raynaud's phenomenon, cold hands and feet Respiratory, thoracic and mediastinal disorders
Bronchospasm (predominately in patients with pre-existing bronchospastic

disease), dyspnoea,cough
Gastrointestinal disorders
Dysgeusia, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting Skin and subcutaneous tissue disorders
Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash
Musculoskeletal and connective tissue disorders
Myalgi
Reproductive system and breast disorders Sexual dysfunction, decreased libido
General disorders and administration site conditions Asthenia/fatigue
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 Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose

Symptoms of systemic timolol overdose include bradycardia, hypotension, bronchospasm, and cardiac arrest. If these symptoms occur, treatment should be symptomatic and supportive. In cases of latanoprost overdose, no ocular or systemic adverse effects are known other than ocular irritation and conjunctival hyperaemia.
If latanoprost is accidentally ingested orally the following information may be useful: Treatment:
Gastric lavage if needed. Symptomatic treatment. Latanoprost is extensively 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. These events were mild to moderate in severity and resolved without treatment, within 4 hours after terminating the infusion.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Ophthalmological-beta-blocking agents - timolol, combinations ATC code: S01ED51
Mechanism of action
Loprostan consists of two components: latanoprost and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by different mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone.
Latanoprost, a prostaglandin F2alpha analogue, is a selective prostanoid FP receptor agonist that reduces the IOP by increasing the outflow of aqueous humour. The main mechanism of action is increased uveoscleral outflow. Additionally, some increase in outflow facility (decrease in trabecular outflow resistance) has been reported in man. Latanoprost has no significant effect

on the production of aqueous humour, the blood-aqueous barrier or the intraocular blood circulation. 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. Timolol is a beta-1 and beta-2 (non-selective) adrenergic receptor blocking agent that has no significant intrinsic sympathomimetic, direct myocardial depressant or membrane- stabilising activity. Timolol lowers IOP by decreasing the formation of aqueous in the ciliary epithelium.
The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable. Timolol has not been found to significantly affect the permeability of the blood-aqueous barrier to plasma proteins. In rabbits, timolol was without effect on the regional ocular blood flow after chronic treatment.

5.2 Pharmacokinetic properties

Latanoprost

Latanoprost is an isopropyl ester prodrug, which per se is inactive but after hydrolysis by esterases in the cornea to the acid of latanoprost, becomes biologically active. The prodrug is well absorbed through the cornea and all drug that enters the aqueous humor is hydrolysed during the passage through the cornea of human. maximum concentration in the aqueous humour, approximately 15-30 ng/mL, is reached about 2 hours after topical administration of latanoprost alone.
After topical ocular administration the systemic bioavailability of the acid of latanoprost is 45%. The acid of latanoprost has a plasma protein binding of 87%.
There is practically no metabolism of the acid of latanoprost in the eye. The main metabolism occurs in the liver. The main metabolites, the 1,2-dinor and 1,2,3,4-tetranor metabolites.

Timolol

The maximum concentration of timolol in the aqueous humour is reached about 1 hour after topical administration of eye drops. Part of the dose is absorbed systemically and a maximum plasma concentration of 1 ng/mL is reached 10-20 minutes after topical administration of one eye drop to each eye once daily (300 micrograms/day). The half- life of timolol in plasma is about 6 hours. Timolol is extensively metabolised in the liver. The metabolites are excreted in the urine together with some unchanged timolol.
Loprostan
No pharmacokinetic interactions between latanoprost and timolol were observed, although there was an approximate 2-fold increased concentration of the acid of latanoprost in aqueous humour 1-4 hours after administration of Loprostan compared to monotherapy.

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

- Tween 80

- Polyethylene glycol 400
- Sodium phosphate monobasic
-Sodium phosphate dibasic
-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 at (2-8) °C (in a refrigerator).Once opened the container may be stored at room temperature below 25°C. Protect from light. 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 Loprostan 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

8. Marketing authorization number(s)
H2025/CTD6758/13142

9. Date of first authorization/renewal of the authorization
17/o2/2025

10. Date of revision of the text
21/08/2026.