SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aristo-LATA Latanoprost Eye Drops 0.005% w/v

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL Eye drops, solution contains 50 micrograms latanoprost.
Each drop contains about 1.5 micrograms of latanoprost.

Excipient with known effect
Benzalkonium chloride 0.02% w/v is included as a preservative.
Sodium dihydrogen phosphate monohydrate, 4.60 mg/mL.
Disodium phosphate anhydrous, 4.74 mg/mL.

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 INFORMATION

4.1 Therapeutic indications

Reduction of increased intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension in adults (including the elderly). It may also be used for the reduction of elevated intraocular pressure as an adjunct medical therapy in patients with primary chronic angle closure glaucoma.

Reduction of increased IOP in paediatric patients with increased IOP and paediatric glaucoma.

4.2 Dosage and route of administration

Dosage

Adults (including elderly people):

The recommended dose is one eye drop in the affected eye or eyes, once daily. The best effect is achieved when Latanoprost is administered in the evening.

Aristo-LATA should not be administered more than once daily as more frequent administration reduces the IOP reduction effect.

If a dose is missed, treatment is continued with the next dose as usual.

Paediatric population:
Aristo-LATA eye drops can be used in paediatric patients, with the same dosage as in adults. No data are available for premature infants (with a gestational age of less than 36 weeks). Data from the age group < 1 year (4 patients) are limited (see section 5.1).
Methods of administration
As with all eye drops, to reduce potential systemic absorption, it is recommended that the lacrimal sac be compressed at the medial canthus (lacrimal punctal occlusion) for one minute. This should be performed immediately after instillation of each drop.

Contact lenses should be removed before instillation of eye drops and can be put back in after 15 minutes.

If more than one topical ophthalmic medicinal product is administered, the medicinal products should be administered at least five minutes apart.

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

Latanoprost can gradually change the colour of the eye by increasing the amount of brown pigment in the iris. Before starting treatment, patients should be informed of the possibility of a permanent change in the colour of their eyes. Unilateral treatment can cause permanent heterochromia. Eyelid skin darkening, which may be reversible, has been reported in association with the use of latanoprost.

The change in eye colour has been observed mainly in patients with irises of mixed colours, i.e. blue-brown, grey- brown, yellow-brown or green-brown. In studies with latanoprost, the onset of change is usually observed within the first eight months of treatment, rarely during the second or third year and has not been observed after the fourth year of treatment. The rate of evolution of iris pigmentation decreases with the passage of time and stabilizes at five years. The incidence of increased pigmentation beyond five years has not been estimated. In an open-label, five-year safety study of latanoprost, 33% of patients developed iris pigmentation (see section 4.8). The change in the colour of the iris is of a slight form in most cases and is often not observed clinically. The frequency in patients with irises of mixed colour ranges from 7 to 85%, with the highest frequency in yellow-brown irises. In patients with homogeneously blue eyes no change was observed, and in patients with homogeneously grey, green or brown eyes, this change was rarely observed.

This change is due to an increased content of melanin in the stromal melanocytes of the iris rather than an increase in the number of melanocytes. Typically, brown pigmentation around the pupil spreads concentrically to the periphery in the affected eyes but the whole iris or parts of it can acquire a brownish colour. No further increase in the brown pigment of the iris has been observed after discontinuation of treatment. It has not been associated with any symptoms or pathological changes in clinical studies to date.

Neither the nevi nor the freckles of the iris have been affected by the treatment. Pigment accumulation in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical studies. Based on 5 years of clinical experience, increased iris pigmentation has not been shown to have adverse clinical effects and Latanoprost can be continued if increased iris pigmentation occurs. However, patients should be examined regularly and depending on their clinical status, treatment with Latanoprost may be discontinued.

There is limited experience with Latanoprost in chronic closed-angle glaucoma, open-angle glaucoma in pseudophakic patients and pigmentary glaucoma. There is no experience with Latanoprost in inflammatory and neovascular glaucoma or in inflammatory eye conditions. Latanoprost has little or no effect on the pupil of the eye, however there is no experience in cases of acute attacks of closed-angle glaucoma. Therefore, it is recommended that the use of Latanoprost is applied with caution in these cases until more experience is gained.

There is limited data from studies on the use of Latanoprost in 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 virus keratitis and in patients with a history of recurrent herpetic keratitis particularly associated with prostaglandin analogues.

Macular oedema have been reported (see section 4.8) mainly in patients with aphakia, patients with pseudophakia and 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 patients with aphakia, patients with pseudophakia and ruptured posterior capsule or anterior chamber intraocular lens, or in patients with known risk factors for cystoid macular oedema.

In patients with known predisposing risk factors for iritis/uveitis, Latanoprost may be used with caution.

There is limited experience in patients with asthma, however some cases of asthma exacerbation and/or dyspnoea have been reported after the product was placed on the market. Patients with asthma should be treated with caution until there is sufficient experience (see also section 4.8).

Periorbital skin discolouration has been observed, with most reports in Japanese patients. Experience to date shows that periorbital skin discolouration is not permanent, and in some cases has recurred while continuing treatment with Latanoprost.

Latanoprost can gradually change eyelashes and thin hairs in the treated eye and periocular structures. These changes include increasing the length, thickness, pigmentation and number of eyelashes or hairs as well as the growth of eyelashes in the wrong direction. Changes in eyelashes are reversible with cessation of treatment.

Preservative

Aristo-LATA contains benzalkonium chloride, which is often used as a preservative in ophthalmic products. From the limited data available, there are no differences in the adverse reaction profile of children compared to that of adults. In general, however, children's eyes manifest a stronger reaction to any stimulus than the eyes of adults. Irritation can have an effect on compliance with treatment in children. Benzalkonium chloride has been reported to cause eye irritation, dry eye symptoms and may affect the tear membrane and corneal surface. It should be used with caution in patients with dry eye and in patients in whom the cornea may be damaged. Patients should be monitored in cases of prolonged use. Because benzalkonium chloride can be absorbed by contact lenses, these must be removed before use of Aristo- LATA but may be worn again after 15 minutes (see section 4.2).

Paediatric population

Efficacy and safety data from the age group < 1 year (4 patients) are very limited (see section 5.1). No data are available for premature infants (with a gestational age of less than 36 weeks).

In children from 0 to < 3 years old, suffering mainly from primary congenital glaucoma (PSC), surgery (e.g. trabeculectomy/goniotomy) remains first-line treatment.

Long-term safety in children has not been established at present.

4.5 Interactions with other medicinal products and other forms of interaction

There is no definitive evidence of interactions.

There have been reports of paradoxical increases in IOP following simultaneous 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 been carried out only in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy There are no adequate and well-controlled studies in pregnant women. Latanoprost should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see section 5.3).

Lactation
Latanoprost and its metabolites can pass into breast milk, so Latanoprost should be used with caution in nursing women.

Fertility
In animal studies, latanoprost has not been found to have effects on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Latanoprost has minor influence on the ability to drive and use machines.
Similar to other ophthalmic preparations, instillation of eye drops may cause transient blurred vision. Until the symptom subsides, patients should not drive or operate machinery.

4.8 Adverse reactions

Tabulated classification of adverse reactions

Category/ organic system	**Common ≥1/100 to < 1/10**	**Uncommon ≥1/1,000 to 1/100.**	**Rare ≥1/10,000 to 1/1.000.**	**Frequency Not Known (cannot be estimated from available data)**
Infections and infestations				Herpetic keratitis*
Nervous system disorders		Headache*, dizziness*		
Eye disorders	Eye irritation (burning, grittiness, itching, stinging and foreign body sensation); eye pain; eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes)*; Ocular hyperaemia; iris hyperpigmentation ; blepharitis; conjunctivitis*	Macular oedema including cystoid mucular oedema*, photophobia*; eyelid oedema; keratitis*; uveitis*	Iritis*, corneal oedema*	Punctate keratitis*; corneal erosion*; trichiasis*; vision blurred*; periorbital and lid changes resulting in deepening of the eyelid sulcus*; darkening of the palpebral skin of the eyelids*; localised skin reaction on the eyelids*; iris cyst*; pseudopemphigoid of the ocular conjunctiva*
Cardiac disorders		Angina, Palpitations*		Unstable angina*
Respiratory, thoracic and Mediastinal disorders		Asthma*, dyspnoea*		Asthma aggravation*; acute asthma attacks
Skin and subcutaneous tissue disorders		Rash	Pruritus	
Musculoskeletal and connective tissue disorders		Myalgia*, arthralgia*		
General disorders and administration site conditions		Chest pain*		

Gastrointestinal disorders		Nausea*	Vomiting*	

*Adverse reaction (AR) of a medicinal product identified after marketing

Adverse reactions reported with the use of eyedrops containing phosphate buffers
Cases of corneal calcification in association with the use of phosphate-containing eye drops have been reported very rarely in some patients with significantly damaged corneas.

Paediatric population
In two short-term clinical trials (≤12 weeks), involving 93 (25 and 68) paediatric patients, the safety profile was similar to that of adults and no new adverse reactions were identified. Short-term safety profiles in different paediatric subgroups were also similar (see section 5.1). The adverse reactions observed more frequently in the paediatric population than in adults were: nasopharyngitis and pyrexia.

4.9 Overdose

Symptoms
Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects have been observed from Latanoprost overdose.

Addressing an overdose
If Latanoprost is accidentally taken orally, the following information may be useful: Each vial contains 125 micrograms of latanoprost. Over 90% is metabolized during the first passage through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers did not cause symptoms, however the dose of 5.5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flashes and sweating. In monkeys latanoprost has been injected intravenously at doses up to 500 micrograms/kg without significant effect on the cardiovascular system.

Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, latanoprost did not cause bronchoconstriction when applied topically to the eyes at a dose of seven times the clinical dose of Latanoprost.

In case of overdose with Latanoprost, treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmic, antiglaucoma preparations and reducers, prostaglandin analogues.
ATC Code: S01EE01

The active substance latanoprost, prostaglandin F_{2a} analogue, is a selective prostanoid FP receptor agonist that reduces intraocular pressure by increasing the outflow of aqueous humour. The decrease in intraocular pressure in humans begins approximately three to four hours after administration, and the maximum effect is achieved after 8-12 hours. Pressure reduction is maintained for at least 24 hours.

Animal and human studies suggest that the main mechanism of its action is increased uveoscleral outflow, although some increase in ease of outflow (decrease in outflow resistance) has been reported in humans.

Pivotal studies have shown that Latanoprost is effective on its own. In addition, clinical studies have been conducted to investigate its use in combination. These include studies from which latanoprost appears to be effective in combination with beta-adrenergic antagonists (timolol). Short-term studies (duration 1 or 2 weeks) suggest that latanoprost activity is additive in combination with adrenergic agonists (dipivalyl epinephrine), carbonic anhydrase inhibitors (acetazolamide) and at least partially additive with cholinergic agonists (pilocarpine).

Clinical studies have shown that latanoprost has no significant effect on aqueous humour production. No effect of latanoprost on the haemato-aqueous barrier has been observed.

Latanoprost showed negligible or no effect on intraocular circulation when used at its clinical dose and was studied in monkeys. However, mild to moderate conjunctival or epidural hyperaemia may occur during topical treatment.

Chronic treatment with latanoprost in the eyes of monkeys that had undergone extracapsular lens removal did not affect retinal blood vessels, as established by fluoresein angiography.

Latanoprost did not induce leakage of fluoresein in the posterior segment in pseudophakic human eyes during short-term therapy.

At clinical doses latanoprost was not found to have any significant pharmacological effects on the cardiovascular or respiratory system.

Paediatric population
The efficacy of latanoprost in paediatric patient≤s 18 years of age was demonstrated in a 12-week, double-blind, clinical study of latanoprost compared to timolol in 107 patients diagnosed with ocular hypertension and paediatric glaucoma. Newborns needed to have a gestational age of at least 36 weeks. Patients received either latanoprost 50 mcg/ml once daily or timolol 0.5% (or alternatively 0.25% for subjects less than 3 years of age) twice daily. The primary efficacy endpoint was the mean decrease in intraocular pressure (IOP) from baseline to Week 12 of the study. Mean values of reduction in intraocular pressure in the latanoprost and timolol groups were similar. In all age groups studied (ages 0 to < 3 years, 3 to < 12 years and 12 to 18 years) mean reduction in intraocular pressure at Week 12, in the latanoprost group, was similar to that in the timolol group. However, efficacy data in the age group 0 - < 3 years were based on only 13 patients for latanoprost and no relevant efficacy was demonstrated from the 4 patients representing the 0 - < 1 years age group in the paediatric clinical study. No data are available for premature infants (with a gestational age of less than 36 weeks).

Reductions in intraocular pressure in patients in the subgroup with primary congenital/infantile glaucoma were similar between the latanoprost group and the timolol group. The subgroup with non-primary congenital glaucoma (e.g. juvenile open-angle glaucoma, aphakic glaucoma) showed similar results to the subgroup of primary congenital glaucoma.

Clinical studies of latanoprost in primary chronic angle closure glaucoma have been limited to 12 weeks. Clinical efficacy and safety in patients with primary chronic angle glaucoma have not been established beyond 12 weeks.

The effect on intraocular pressure was observed after the first week of treatment (see Table) and was maintained throughout the 12 weeks of the study, as in adults.

Table: Intraocular pressure reduction (mmHg), at Week 12, by active treatment group and diagnosis at baseline

	Latanoprost N=53		**Timolol N=54**	
Mean starting value (SE)	27.3 (0.75)		27.8 (0.84)	
Week 12, change from baseline Mean† (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**
Mean starting value (SE)	26.5 (0.72)	28.2 (1.37)	26.3 (0.95)	29.1 (1.33)
Week 12, change from baseline Mean† (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 analysis of covariance (ANCOVA) model.
* PCG: Primary Congenital Glaucoma
** Non-PCG: Non-Primary Congenital Glaucoma.

5.2 Pharmacokinetic properties

Absorption
Latanoprost (molecular weight 432.58) is a prodrug of isopropyl ester which is inert as it is, but after hydrolysis in latanoprost acid becomes biologically active.

The prodrug shows good absorption through the cornea, and the entire amount of the drug entering the aqueous humour is hydrolysed during its passage through the cornea.

Distribution
Clinical studies in humans show that the maximum concentration in aqueous humour is reached within approximately two hours after topical administration. After topical application in monkeys, latanoprost is mainly distributed in the anterior segment, conjunctiva and eyelids. Only minimal amounts of the medicinal product reach the posterior segment.

Biotransformation and elimination
There is almost no metabolism of latanoprost acid in the eye. The main metabolism takes place in the liver. The plasma half-life is approximately 17 minutes in humans. The major metabolites, 1,2-dinor and 1,2,3,4-tetranor metabolites exert little or no biological activity in animal studies and are excreted mainly in urine.

Paediatric population
An open-label pharmacokinetic study of latanoprost acid plasma concentrations was conducted in 22 adult and 25 paediatric patients (age from birth to < 18 years) with ocular hypertension and glaucoma; All age groups were treated with latanoprost 50 mcg/ml, one drop daily, in each eye, for at least 2 weeks. Systemic exposure of latanoprost acid was approximately 2-fold higher in children aged 3 to < 12 years and 6-fold higher in children aged < 3 years, compared to adults, but a wide margin of safety has been maintained with respect to systemic adverse reactions (see section 4.9). The median time to reach peak plasma concentrations was 5 minutes post-dose for all age groups. The mean plasma half-life was short (< 20 min), similar for paediatric and adult patients and did not result in latanoprost acid concentration in systemic circulation in steady-state conditions.

5.3 Preclinical safety data

The ocular as well as systemic toxicity of latanoprost has been investigated in many animal species. In general, latanoprost exhibits good tolerance with a safety margin between clinical ocular dose and systemic toxicity at least 1,000 fold. High doses of latanoprost, approximately 100 times the clinical dose/kg body weight, administered intravenously to unanaesthetised monkeys, have been shown to increase the speed of breathing, possibly reflecting some short-term bronchoconstriction. No sensitising properties were demonstrated in studies with latanoprost in animals.

No toxic effect on the eye was found at doses up to 100 micrograms/eye/day in rabbits or monkeys (clinical dose is approximately 1.5 micrograms/eye/day). However, in monkeys, it was shown that latanoprost causes increased pigmentation of the iris.

The mechanism of increased pigmentation appears to be the stimulation of melanin production in melanocytes of the iris. Exogenous (productive) changes have not been observed. The change in the colour of the iris can be permanent.

In chronic ocular toxicity studies the administration of latanoprost at a dose of 6 mcg/eye/day has also been shown to induce increased palpebral fissure. This effect is reversible and is observed at doses higher than the clinical dose level. This effect has not been observed in humans.

Latanoprost was negative in bacterial reverse mutation tests, gene mutation in mouse lymphoma and mouse micronucleus assay. In vitro chromosomal aberrations were observed with human lymphocytes. Similar effects were observed with prostaglandin F_{2a}, prostaglandin found in nature, and this suggests that this is a class effect.

Additional mutagenicity studies in vitro/in vivo unscheduled DNA synthesis in rats were negative and indicate that latanoprost has no mutagenic potential. Carcinogenicity studies in mice and rats were negative.

It has been found that latanoprost has no effect on the fertility of male or female experimental animals. In the embryotoxicity study in rats no embryotoxicity was observed at intravenous doses (5, 50 and 250 mcg/kg/day) of latanoprost. However, latanoprost produced embryolethal effects in rabbits at doses of 5 mcg/kg/ day and higher.

The dose of 5 mcg/kg/day (approximately 100 times the clinical dose) produced significant embryofetal toxicity characterised by an increased incidence of late resorption and abortion as well as reduced foetal weight.

There was no evidence of teratogenic potential.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

Sodium chloride
Benzalkonium chloride
Sodium dihydrogen phosphate monohydrate
Disodium Phosphate Anhydrous
Sodium hydroxide and/or hydrochloric acid 1N
Water for injections

6.2 Incompatibilities

In vitro studies have shown that precipitation occurs when thiomersal containing eye drops are mixed with Latanoprost. If such medicinal products are used, eye drops should be administered at least five minutes apart.

6.3 Shelf life

Shelf life: 3 years

Shelf life after first opening the container: 28 days.

6.4 Special precautions during storage of the product

Store in a refrigerator (2° to 8°C). Do not freeze.

Keep the vial in the outer carton in order to protect from light.

After first opening the container: Store at room temperature ≤25ºC and should be used within four weeks.

6.5 Nature and components of the container

Polyethylene dropper vial (5 ml) with a screw cap and a safety ring.

Each dropper vial contains 2.5 ml solution for eye drops.

Package Sizes: 1 x 2.5 ml

6.6 Special precautions for disposal and other handling

No special precautions.

7. PRODUCT OWNER

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8. MANUFACTURER

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9. DATE OF REVISION OF THE TEXT

01/2024