1. NAME OF THE MEDICINAL PRODUCT

Ablatan 50 micrograms/ml eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml eye drops solution contains 50 micrograms of latanoprost.

One drop contains approximately 1.5 micrograms of latanoprost.

Excipient with known effect:

Each ml of solution contains 0.2 mg benzalkonium chloride and 8.77 mg phosphates.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.

The solution is a clear colourless liquid.

Osmolality 260-330 mOsmol/kg, pH 6.0-7.5.

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

Posology

Adults (including the elderly)
Recommended therapy is one eye drop in the affected eye(s) once daily. Optimal effect is obtained if Ablatan is administered in the evening.

The dosage of Ablatan 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
Ablatan 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 are limited (see section 5.1).

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 listed in section 6.1.

4.4 Special warnings and precautions for use

Iris pigmentation changes

Ablatan 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.

In a long-term observational paediatric study evaluating hyperpigmentation changes in the eye among patients with paediatric glaucoma, iris colour darkening and localised iris pigmentation were observed to a slightly greater extent in patients exposed to latanoprost group compared with the unexposed group (see section 5.1).

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 Ablatan can be continued if iris pigmentation ensues. However, patients should be monitored regularly and if the clinical situation warrants, Ablatan 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 Ablatan 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. Ablatan should be used with caution in these patients.

Ablatan 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). Ablatan 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, Ablatan 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, 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.

Preservative
Ablatan 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 Ablatan but may be reinserted after 15 minutes (see section 4.2).

Paediatric population

Efficacy and safety data in the age group < 1 year 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 primary congenital glaucoma (PCG), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Definitive medicinal product 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 Fertility, 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 established. It has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate. Therefore, this medicine should not be used during pregnancy.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

Ablatan 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

Bimatoprost/Timolol medicinal product

Summary of the safety profile

The adverse reactions reported in clinical studies using bimatoprost/timolol were limited to those earlier reported for either of the single active substances bimatoprost and timolol. No new adverse reactions specific for bimatoprost/timolol have been observed in clinical studies.

The majority of adverse reactions reported in clinical studies using bimatoprost/timolol were ocular, mild in severity and none were serious. Based on 12-month clinical data, the most commonly reported adverse reaction was conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in approximately 26 % of patients and led to discontinuation in 1.5 % of patients.

Tabulated list of adverse reactions

Table 1 presents the adverse reactions that have been reported during clinical trials with bimatoprost/timolol formulations (multi-dose and single-dose) (within each frequency

grouping, adverse reactions are presented in order of decreasing seriousness) or in the post-marketing period.

The frequency of possible adverse reactions listed below is defined using the following convention:

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
Not known	Frequency cannot be estimated from available data

Table 1

System Organ Class	**Frequency**	**Adverse reaction**
Immune system disorders	Not known	Hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy
Psychiatric disorders	Not known	Insomnia[2], nightmare[2]
Nervous system disorders	Common	Headache
	Not known	Dysgeusia[2], dizziness
Eye disorders	Very common	Prostaglandin analogue periorbitopathy, conjunctival hyperaemia
	Common	Punctuate keratitis, corneal erosion[2], burning sensation[2], conjunctival irritation[1], eye pruritus, stinging sensation in the eye[2], foreign body sensation, dry eye, erythema of eyelid, eye pain, photophobia, eye discharge, visual disturbance[2], eyelid pruritus, visual acuity worsened[2], blepharitis[2], eyelid oedema, eye irritation, lacrimation increased, growth of eyelashes
	Uncommon	Iritis[2], conjunctival oedema[2], eyelid pain[2], abnormal sensation in the eye[1], asthenopia, trichiasis[2], iris hyperpigmentation[2], eyelid retraction[2], eyelash discolouration (darkening)[1]
	Not known	Cystoid macular oedema[2], eye swelling, vision blurred[2], ocular discomfort
Cardiac disorders	Not known	Bradycardia
Vascular disorders	Not known	Hypertension
Respiratory, thoracic and mediastinal disorders	Common	Rhinitis[2]
	Uncommon	Dyspnoea
	Not known	Bronchospasm (predominantly in patients with pre-

System Organ Class	Frequency	Adverse reaction
		existing bronchospastic disease)[2], asthma
Skin and subcutaneous tissue disorders	Common	Blepharal pigmentation[2], hirsutism[2], skin hyperpigmentation (periocular)
	Not known	Alopecia, skin discoloration (periocular)
General disorders and administration site conditions	Not known	Fatigue

[1] adverse reactions only observed with bimatoprost/timolol single-dose formulation

[2] adverse reactions only observed with bimatoprost/timolol multi-dose formulation

Like other topically applied ophthalmic drugs, Abimet Duo (bimatoprost/timolol) is absorbed into the systemic circulation. Absorption of timolol may cause similar undesirable effects as seen with systemic beta-blocking agents. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Additional adverse reactions that have been seen with either of the active substances (bimatoprost or timolol), and may potentially occur also with bimatoprost/timolol are listed below in Table 2:

Table 2

System Organ Class	Adverse reaction
Immune system disorders	Systemic allergic reactions including anaphylaxis[1]
Metabolism and nutrition disorders	Hypoglycaemia[1]
Psychiatric disorders	Depression[1], memory loss[1], hallucination[1]
Nervous system disorders	Syncope[1], cerebrovascular accident[1], increase in signs and symptoms of myasthenia gravis[1], paraesthesia[1], cerebral ischaemia[1]
Eye disorders	Decreased corneal sensitivity[1], diplopia[1], ptosis[1], choroidal detachment following filtration surgery (see section 4.4)[1], keratitis[1], blepharospasm[2], retinal haemorrhage[2], uveitis[2]
Cardiac disorder	Atrioventricular block[1], cardiac arrest[1], arrhythmia[1], cardiac failure[1], congestive heart failure[1], chest pain[1], palpitations[1], oedema[1]
Vascular disorders	Hypotension[1], Raynaud's phenomenon[1], cold hands and feet[1]
Respiratory, thoracic and mediastinal disorders	Asthma exacerbation[2], COPD exacerbation[2], cough[1]
Gastrointestinal disorders	Nausea[1,2], diarrhoea[1], dyspepsia[1], dry mouth[1], abdominal pain[1],

	vomiting[1]
Skin and subcutaneous tissue disorders	Psoriasiform rash[1] or exacerbation of psoriasis[1], skin rash[1]
Musculoskeletal and connective tissue disorders	Myalgia[1]
Reproductive system and breast disorders	Sexual dysfunction[1], decreased libido[1]
General disorders and administration site conditions	Asthenia[1,2]
Investigations	Liver function tests (LFT) abnormal[2]

[1] adverse reactions observed with Timolol

[2] adverse reactions observed with Bimatoprost monotherapy

Description of selected adverse events

Prostaglandin analogue periorbitopathy (PAP)

Prostaglandin analogues including Abimet Duo can induce periorbital lipodystrophic changes which can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involution of dermatochalasis and inferior scleral show. Changes are typically mild, can occur as early as one month after initiation of treatment with Abimet Duo, and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discoloration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.

Iris hyperpigmentation

Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long-term effects of increased iris pigmentation are not known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts become more brownish. Neither naevi nor freckles of the iris appear to be affected by the treatment. At 12 months, the incidence of iris hyperpigmentation with bimatoprost 0.1 mg/ml eye drops, solution was 0.5%. At 12 months, the incidence with bimatoprost 0.3 mg/ml eye drops, solution was 1.5% (see section 4.8 Table 2) and did not increase following 3 years treatment.

Adverse reactions reported in phosphate containing eye drops

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: Yellow Card Scheme website: http://www.mhra.gov.uk/yellowcard
or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

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

Treatment

If Ablatan 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 overdose with Ablatan occurs, treatment should be symptomatic.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmological,– beta-blocking agents –ATC code: S01ED51

Mechanism of action

Abimet Duo consists of two active substances: bimatoprost and timolol. These two components decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone. Bimatoprost/Timolol has a rapid onset of action.

Bimatoprost is a potent ocular hypotensive active substance. It is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) that does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet

been structurally identified. The mechanism of action by which bimatoprost reduces intraocular pressure in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a $beta_1$ and $beta_2$ non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation. 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.

Clinical effects

The IOP-lowering effect of Bimatoprost/Timolol is non-inferior to that achieved by adjunctive therapy of bimatoprost (once daily) and timolol (twice daily).

Existing literature data for bimatoprost/timolol suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing.

Paediatric population

The safety and efficacy of Abimet Duo in children aged 0 to 18 years has not been established.

5.2 Pharmacokinetic 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

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 minor 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.

Paediatric population

An open-label pharmacokinetic study of plasma latanoprost acid concentrations was undertaken in 22 adults and 25 paediatric patients (from birth to <18 years of age) with ocular hypertension and glaucoma. All age groups were treated with latanoprost 50 mcg/mL one drop daily in each eye for a minimum of 2 weeks. Latanoprost acid systemic exposure was approximately 2-fold higher in 3 to <12 year old and 6-fold higher in children <3 years old compared with adults, but a wide safety margin for systemic adverse effects was maintained (see section 4.9). Median time to reach peak plasma concentration was 5 minutes post-dose across all age groups. The median plasma elimination half-life was short (<20 minutes), similar for paediatric and adult patients, and resulted in no accumulation of latanoprost acid in the systemic circulation under steady-state conditions.

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.

No teratogenic potential has been detected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Sodium dihydrogen phosphate dihydrate

Disodium phosphate dodecahydrate

Sodium chloride

Purified water

6.2 Incompatibilities

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

6.3 Shelf life

Unopened bottle: 3 years

After first opening: 4 weeks

6.4 Special precautions for storage

Unopened bottle: Store in a refrigerator (2–8 °C).

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

After first opening the bottle: Do not store above 25 °C. Four weeks after the first opening this product should be disposed of, even if it has not been completely used up.

6.5 Nature and contents of container

LDPE bottle with HDPE screw cap and LDPE dropper.

Each bottle contains 2.5 ml eye drops solution corresponding to approximately 86 drops of solution.

Pack sizes: 1 × 2.5 ml, 3 × 2.5 ml and 6 × 2.5 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Axunio Pharma GmbH

Van-Der-Smissen-Strasse 1

22767 Hamburg, Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 47848/0052

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/09/2025

10 DATE OF REVISION OF THE TEXT

12/05/2026