Approved Professional Information for Medicines for Human Use:

AGLATAN

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AGLATAN 50 µg/mL and 5 mg/mL, EYE DROPS, SOLUTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AGLATAN Eye drops, solution

Each millilitre contains latanoprost 50 µg and timolol maleate equivalent to 5 mg timolol.

Contains Preservative: benzalkonium chloride 0,02 % *m/v*

Contains Phosphate Buffers: disodium phosphate dodecahydrate 11,85 mg/mL and sodium dihydrogen phosphate dihydrate 5,20 mg/mL

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

AGLATAN eye drops, solution is clear, colourless and sterile aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who are not controlled on, or are intolerant to, monotherapy with compounds other than latanoprost and timolol.

4.2 Posology and method of administration

Posology

Use in adults (including the elderly):

One drop in the affected eye(s) once daily.

The dosage of AGLATAN should not exceed once daily since it has been shown that more frequent administration of latanoprost decreases the intraocular pressure lowering effect.

If one dose is missed, treatment should continue with the next dose as planned.

If more than one topical ophthalmic medicine is being used, they should be administered at least 5 minutes apart.

Paediatric population

The safety and efficacy of AGLATAN in children and adolescents has not been established.

Method of administration

AGLATAN is for ocular administration.

4.3 Contraindications

- Hypersensitivity to latanoprost, timolol maleate, benzalkonium chloride or to any of the excipients listed in section 6.1.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, chronic obstructive pulmonary disease.

- Sinus bradycardia, second or third degree atrioventricular block, cardiac failure, cardiogenic shock.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Systemic effects

AGLATAN is absorbed systemically. Due to the beta-adrenergic component timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-adrenergic blocking medicines may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

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.

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.

Aggravation of Prinzmetal’s angina, hypotension, bradycardia, cardiac reactions, and less frequently, death in association with cardiac failures have been reported following administration of timolol.

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, as aggravation of peripheral and central circulatory disorders may occur after topical application of timolol maleate as in AGLATAN.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. AGLATAN should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD).

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 increase the hypoglycaemic effect of medicines used to treat diabetes and may mask the signs and symptoms of acute hypoglycaemia.
Beta-blockers may also mask the signs of hyperthyroidism. Abrupt withdrawal of therapy may precipitate a worsening of this condition.

Corneal diseases

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

Other beta-blocking medicines

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

should be closely observed. The use of two topical beta-adrenergic blocking medicines 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.

A gradual withdrawal of beta-adrenergic blocking medicines prior to major surgery should be considered. Beta-adrenergic blocking medicines impair the ability of the heart to respond to beta- adrenergically mediated reflex stimuli, which may augment the risk of general anaesthesia in surgical procedures. Protracted severe hypotension during anaesthesia and difficulty restarting and maintaining the heartbeat have been reported. During surgery, the effects of beta-adrenergic blocking medicines may be reversed by sufficient doses of adrenergic agonists.

Concomitant therapy

Timolol may interact with other medicines see section 4.5. The concomitant use of AGLATAN with hypoglycaemic medicines, phenothiazines and various anti-dysrhythmic medicines may have interactions with life-threatening consequences.

Other prostaglandin analogues

The concomitant use of two or more prostaglandins, prostaglandin analogues, or prostaglandin derivatives is not recommended (see section 4.5).

Timolol maleate has been reported to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms (e.g. diplopia, ptosis, generalised weakness).

Iris pigmentation changes

Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Similar to experience with latanoprost eye drops, it is reported that an increased iris pigmentation was seen in patients treated with latanoprost-timolol for up to one year. This effect has predominantly been seen in patients with mixed coloured irides that contain the colour brown at baseline, i.e., green-brown, yellow-brown or blue/grey-brown, and is due to increased melanin content in the stromal melanocytes of the iris, rather than to an increase in the 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. In patients with homogeneously blue, grey, green or brown eyes, the change has only less frequently been seen during two years of treatment in reported clinical trials with latanoprost.

Onset of increased iris pigmentation typically occurs within the first year 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 by five years. The effects of increased pigmentation beyond five years have not been evaluated.

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.

IOP reduction was similar in patients regardless of the development of increased iris pigmentation. Therefore, treatment with latanoprost can be continued in patients who develop increased iris pigmentation. These patients should be examined regularly and, depending on the clinical situation, treatment may be stopped.

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.

Eyelid and eyelash changes

Eyelid skin darkening, which may be reversible, has been reported in association with the use of latanoprost.

Latanoprost may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, and number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.

Glaucoma

There is no documented experience with latanoprost in inflammatory, neovascular, or chronic angle closure glaucoma, in open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. Latanoprost has no or little effect on the pupil but there is no documented experience in acute attacks of closed angle glaucoma. Therefore, it is recommended that AGLATAN should be used with caution in these conditions until more experience is obtained.

Herpetic keratitis

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

Macular oedema, including cystoid macular oedema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema. AGLATAN should be used with caution in these patients.

Paediatric Population

See section 4.2.

Excipients: Benzalkonium chloride

AGLATAN contain benzalkonium chloride

Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. Contact lenses should be removed before using this medicine and put them back 15 minutes afterwards. Benzalkonium chloride may also cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. It should be used with caution in dry eye patients and in patients where the cornea may be compromised due to extensive ocular disease.

Patients should be monitored in case of prolonged use.

4.5 Interaction with other medicines and other forms of interaction

No specific medicine interaction studies have been performed with AGLATAN.

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.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic betablockers solution are administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking medicines, antidysrhythmics (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 beta-blockade may be potentiated when AGLATAN is given to patients already receiving an oral beta-adrenergic blocking medicine, and the use of two or more topical beta-adrenergic blocking medicines 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 beta-blockers.

Beta-blockers may increase the hypoglycaemic effect of anti-diabetic medicines. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).
The concomitant use of AGLATAN with hypoglycaemic medicines, phenothiazines and various anti-dysrhythmic medicines may have interactions with life-threatening consequences.

4.6 Fertility, pregnancy and lactation

AGLATAN is contraindicated in pregnancy and breastfeeding (see section 4.3).

Pregnancy

Latanoprost

There are no adequate data from the use of latanoprost in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Timolol

There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy.

Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when betablockers have been administered until delivery.

Consequently, AGLATAN should not be used during pregnancy.

Breastfeeding

AGLATAN should not be used in breastfeeding women, or breastfeeding should be stopped as timolol is excreted in breast milk and latanoprost and its metabolites may pass into breast milk (see section 4.3).

Fertility

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

4.7 Effects on ability to drive and use machines

AGLATAN has minor influence on the 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 reactions relate to the ocular system. Patients have developed increased iris pigmentation, which may be permanent (see section 4.4). Ocular adverse reactions are generally transient and occur on dose administration. For timolol, the most serious adverse reactions are systemic in nature, including bradycardia, dysrhythmia, congestive heart failure, bronchospasm and allergic reactions.

Timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta blocking medicines. 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.

Adverse reactions for latanoprost- timolol			
System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations	Infection, sinusitis, upper respiratory tract infection		
Metabolism and nutrition disorders	Diabetes mellitus, hypercholesterolaemia		
Psychiatric disorders	Depression		

Nervous system disorders		Headache	
Eye disorders	Iris hyperpigmentation Eye pain, eye irritation (including stinging, burning, itching, foreign body sensation), abnormal vision, cataract, conjunctival disorder, errors of refraction, keratitis, photophobia, visual field defect	Corneal disorders, conjunctivitis, blepharitis, eye hyperaemia, vision blurred, lacrimation increased	
Vascular disorders	Hypertension		
Skin and subcutaneous tissue disorders	Hypertrichosis	Rash, pruritus	

Musculoskeletal and connective tissue disorders	Arthritis		

Adverse Reaction: Latanoprost			
System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations			Herpetic keratitis
Nervous system disorders			Dizziness
Eye disorders	Eye irritation (burning, grittiness, itching, stinging and foreign body sensation) Eyelid oedema; transient punctate epithelial erosions		Eyelash and vellus hair changes (increased length, thickness, pigmentation and number of eyelashes),

			vision blurred, iritis/uveitis, macular oedema including cystoid macular oedema, corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation
Cardiac disorders			Angina; angina unstable; palpitations
Respiratory, thoracic and mediastinal disorders			Asthma, dyspnoea, asthma aggravation, acute asthma attacks
Skin and subcutaneous tissue disorders	Skin rash		Localised skin reaction on eyelids, darkening of

			palpebral skin of the eyelids
Musculoskeletal and connective tissue disorders			Muscle/joint pain
General disorders and administration site conditions			Non-specific chest pain

Adverse Reaction: Timolol Maleate (ocular administration)			
System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Immune system disorders			Systemic allergic reactions including anaphylactic reaction,

			angioedema, urticaria, localised and generalised rash, pruritus
Metabolism and nutrition disorders			Anorexia, masked symptoms of hypoglycaemia in diabetic patients
Psychiatric disorders			Behavioural changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss, decreased libido, insomnia, nightmares, depression
Nervous system disorders			Dizziness, paraesthesia, somnolence, cerebral ischaemia, cerebral vascular accident, increase in signs and symptoms of myasthenia gravis, syncope, headache

Eye disorders			Visual disturbance including refractive changes and diplopia, ptosis, cystoid macular oedema, decreased corneal sensitivity, choroidal detachment following filtration surgery, corneal erosion, keratitis, signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing and redness), dry eyes, blepharitis
Ear and labyrinth disorders			Tinnitus
Cardiac disorders			Cardiac arrest, atrioventricular block, congestive heart failure, chest pain, dysrhythmia,

			bradycardia, oedema, palpitations and worsening of angina pectoris
Vascular disorders			Claudication, hypotension, cold hands and feet, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders			Dyspnoea, cough, bronchospasm (predominately in patients with pre-existing bronchospastic disease), nasal congestion, pulmonary oedema, respiratory failure
Gastrointestinal disorders			Diarrhoea, dry mouth, dyspepsia, nausea, retroperitoneal fibrosis, abdominal pain, vomiting, dysgeusia
Skin and subcutaneous tissue disorders			Alopecia pseudopemphigoid, psoriasiform rash or

			exacerbation of psoriasis, skin rash
Musculoskeletal and connective tissue disorders			Systemic lupus erythematosus, myalgia
Reproductive system and breast disorders			Impotence, Peyronie's disease, decreased libido
General disorders and administration site conditions			Asthenia/fatigue, chest pain, oedema

Cases of corneal calcification have been reported less frequently 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

No data are available in humans with regard to overdose with AGLATAN.

Signs and symptoms

Symptoms of systemic timolol overdose are: dizziness, headache, bradycardia, hypotension, bronchospasm and cardiac arrest.

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

In patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost such as contained in AGLATAN when applied topically in the eyes in a dose seven times the clinical dose of latanoprost.

There have been reports of inadvertent overdosage with latanoprost-timolol eye drops, resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking medicines such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest.

Treatment

If symptoms of overdose occur the treatment should be symptomatic and supportive.

If accidentally ingested orally the following information may be useful:

Studies have shown that timolol does not dialyse readily. 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

Category and Class: A 15.4 Ophthalmic preparations: others

Pharmacotherapeutic group: Ophthalmological-beta blocking agents - timolol, combinations

ATC Code: S01ED51

Mechanism of action

AGLATAN consists of two components: latanoprost and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by different mechanisms of action.

Latanoprost, a prostaglandin F2α analogue, is a prostanoid selective prostaglandin F2 (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 activity (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. 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 medicine. Timolol lowers IOP by decreasing aqueous humour formation in the ciliary epithelium. The precise mechanism of action has not been clearly established.

Pharmacodynamic effects

Clinical efficacy and safety

Onset of action of AGLATAN is within one hour, and maximal effect occurs within six to eight hours.

IOP reducing effect has been shown to be present up to 24 hours post dosage after multiple treatments.

5.2 Pharmacokinetic properties

Latanoprost

Absorption

Latanoprost is an isopropyl ester prodrug that 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 medicine that enters the aqueous humour is hydrolysed during the passage through the cornea.

Distribution

Studies in man indicate that the maximum concentration in the aqueous humour, approximately 30 ng/mL, is reached about 2 hours after topical administration of latanoprost alone.

The acid of latanoprost has a plasma clearance of 0,4 L/h/kg and a small volume of distribution, 0,16 L/kg, resulting in a rapid half-life in plasma, of 17 minutes.

Biotransformation and elimination

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, exert no or only weak biological activity in animal studies.

Elimination:

The main metabolites are excreted primarily in the urine.

Timolol

Absorption

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.

Distribution

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).

Biotransformation

The half-life of timolol in plasma is about 4 hours. Timolol is extensively metabolised in the liver

Elimination

The metabolites are excreted in the urine together with some unchanged timolol.

AGLATAN

No pharmacokinetic interactions between latanoprost and timolol were observed, although there is a tendency for increased concentrations of the acid of latanoprost in aqueous humour 1 to 4 hours after administration of AGLATAN compared to monotherapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Disodium phosphate dodecahydrate

Sodium chloride

Sodium dihydrogen phosphate dihydrate

Sodium hydroxide or hydrochloric acid (1M) (pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

Shelf life: 36 months

In-use shelf life: 28 days

6.4 Special precautions for storage

Store in refrigerator at 2 ºC – 8 ºC in the original carton.

Once the bottle is opened the contents must be used within 28 days and may be stored at room temperature at or below 25 ºC.

The bottle must be stored in the original carton to protect it from light.

6.5 Nature and contents of container

AGLATAN eye drops, solution is packed in transparent LDPE bottles with white HDPE screw cap and transparent LDPE dropper insert.

Each bottle contains 2,5 mL or 5 mL eye drops, solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER

51/15.4/0618

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 July 2022

10. DATE OF REVISION OF THE TEXT