SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

XALACOM® Eye Drops

COMPOSITION:

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

Preservative: Benzalkonium chloride 0,02 % m/v.

One drop contains approximately 1,5 µg latanoprost and 150 µg timolol.

XALACOM contains the following inactive ingredients: benzalkonium chloride (0,02 % m/v), disodium phosphate anhydrous, sodium chloride, sodium dihydrogen phosphate monohydrate, water for injections and hydrochloric acid or sodium hydroxide.

PHARMACOLOGICAL CLASSIFICATION:

A 15.4 Ophthalmic preparations: Others

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Mechanism of action:

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

Latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a prostanoid selective prostaglandin F_2 (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 agent. 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 effects:

Onset of action of XALACOM 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.

Pharmacokinetic properties:

Latanoprost:

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 drug that enters the aqueous humour is hydrolysed during the passage through the cornea. 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.

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 and are excreted primarily in the urine.

Timolol:

The maximum concentration of timolol in the aqueous humour is reached about one 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 4 hours. Timolol is extensively metabolised in the liver. The metabolites are excreted in the urine together with some unchanged timolol.

XALACOM:

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 XALACOM compared to monotherapy.

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.

CONTRAINDICATIONS:

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.

Known hypersensitivity to latanoprost, timolol maleate or any other component of this product.

Pregnancy and lactation (see PREGNANCY AND LACTATION).

WARNINGS:

Latanoprost:

Latanoprost may gradually increase the brown pigment of the iris. The eye colour change 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 of the iris and the entire iris or parts of the iris become more brownish. The change in iris colour is mild in the majority of cases and may not be detected clinically. The increase in iris pigmentation in one or both eyes has been documented predominantly in patients who have mixed-colour irides that contain the colour brown at baseline. Neither nevi nor freckles of the iris have been affected by treatment. No accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has been observed in clinical trials.

In a clinical trial designed to assess iris pigmentation over five years, there was no evidence of adverse consequences due to increased pigmentation even when administration of latanoprost

continued. These results are consistent with post-marketing clinical experience since 1996. In addition, 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.

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. During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant colour change may be permanent.

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.

The potential for heterochromia exists for patients receiving unilateral treatment.

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 torn posterior lens capsule, or in patients with known risk factors for macular oedema. Caution is recommended when using XALACOM in these patients.

There is no documented experience with latanoprost-timolol in inflammatory, neovascular, chronic angle closure or congenital glaucoma, in open angle glaucoma of pseudophakic patients and in pigmentary glaucoma. Therefore, it is recommended that latanoprost-timolol should be used with caution in these conditions until more experience is obtained.

Timolol:

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with their topical administration. Patients with a history of severe cardiac disease should be

monitored closely for signs of cardiac failure. The following cardiac and respiratory reactions may occur after topical application of timolol maleate as in XALACOM:

- Aggravation of Prinzmetal's angina
- Aggravation of peripheral and central circulatory disorders
- Hypotension
- Cardiac failure resulting in death
- Severe respiratory reactions, including fatal bronchospasm in patients with asthma
- Bradycardia

The concomitant use of XALACOM with hypoglycaemic agents, phenothiazines and various anti-dysrhythmic agents may have interactions with life-threatening consequences.

A gradual withdrawal of beta-adrenergic blocking agents prior to major surgery should be considered. Beta-adrenergic blocking agents 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 agents may be reversed by sufficient doses of adrenergic agonists.

Beta-adrenergic blocking agents may increase the hypoglycaemic effect of agents used to treat diabetes and can mask the signs and symptoms of hypoglycaemia. They should be used with caution in patients with spontaneous hypoglycaemia or diabetes (especially those with labile diabetes), who are receiving insulin or oral hypoglycaemic agents.

Therapy with beta-adrenergic blocking agents may mask certain signs and symptoms of hyperthyroidism. Abrupt withdrawal of therapy may precipitate a worsening of this condition.

When treated with beta-adrenergic blocking agents, patients with a history of atopy or severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens. They may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

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

Choroidal detachment after filtration procedures has been reported with the administration of ocular hypotensive agents.

Use of contact lenses:

XALACOM contains benzalkonium chloride which may be absorbed by contact lenses. The contact lenses should be removed before instillation of the eye drops and may be reinserted after fifteen minutes.

Use in children:

Safety and effectiveness in children have not been established.

Benzalkonium chloride:

As the possibility of adverse effects on the corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride-preserved ophthalmological preparations cannot be excluded, regular ophthalmological examination is required.

Caution should be exercised in the use of benzalkonium chloride-preserved topical medication over an extended period in patients with extensive ocular surface disease.

INTERACTIONS:

Specific interaction studies have not been performed with XALACOM.

The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when XALACOM 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.

There have been reports of paradoxical elevations in IOP following the concomitant ophthalmic administration of two prostaglandin analogs. Therefore, the use of two or more prostaglandins, prostaglandin analogs, or prostaglandin derivatives is not recommended.

The potential exists for additive effects resulting in hypotension and/or marked bradycardia when eye drops containing timolol are administered with calcium-channel blockers, catecholamine-depleting medicines or beta-blocking agents, anti-arrhythmics (including amiodarone and quinidine), digitalis glycosides, parasympathomimetics, narcotics and monoamine oxidase (MAO) inhibitors.

Although XALACOM alone has little or no effect on pupil size, mydriasis has occasionally been reported when timolol is given with adrenaline.

Beta-blockers may increase the hypoglycaemic effect of anti-diabetic agents (see WARNINGS).

The concomitant use of XALACOM with hypoglycaemic agents, phenothiazines and various anti-arrhythmic agents may have interactions with life-threatening consequences.

PREGNANCY AND LACTATION:

Pregnancy:

The safety in pregnancy has not been established (see CONTRAINDICATIONS).

Lactation:

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

DOSAGE AND DIRECTIONS FOR USE:

The tamper evident overcap should be removed before use.

Use in adults (including the elderly):

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

The dosage of XALACOM 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.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

The adverse events of XALACOM are similar to those reported earlier for latanoprost and timolol. Based on evidence from consecutive photographs, increased iris pigmentation was seen in 16 – 20 % of all patients who received XALACOM eye drops for up to one year.

The most frequent findings of increased iris pigmentation were in patients with green-brown, yellow-brown and blue/grey/brown irides. In patients with homogenously blue, grey, green or brown eyes, the change was only rarely seen.

Darkening, thickening and lengthening of the eye lashes has been reported.

The most frequently reported undesirable effects in clinical trials were irritation of the eye, including stinging, burning and itching, eye hyperaemia, corneal disorders, conjunctivitis, blepharitis, eye pain, headache and skin rash.

The tables below contain side effects categorised as follows utilising the incidence rates: Very common ≥ 1/10 (≥ 10 %); Common ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %); Uncommon ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %); Rare ≥ 1/10 000 and < 1/1000 (≥ 0,01 % and < 0,1 %); Very rare < 1/10 000 (< 0,01 %).

LATANOPROST-TIMOLOL (CLINICAL TRIALS)		
MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Infections and infestations	Common	Infection, sinusitis, upper respiratory tract infection
Metabolism and nutrition disorders	Common	Diabetes mellitus, hypercholesterolaemia
Psychiatric disorders	Common	Depression
Nervous system disorders	Common	Headache
Eye disorders	Very common	Eye irritation, increased iris pigmentation
	Common	Abnormal vision, blepharitis, cataract, conjunctival disorder, conjunctivitis, corneal disorder, errors of refraction, eye hyperaemia, eye pain, keratitis, photophobia, visual field defect
Vascular disorders	Common	Hypertension
Skin and subcutaneous tissue disorders	Common	Hypertrichosis, rash, skin disorder
Musculoskeletal and	Common	Arthritis

connective tissue disorders		
LATANOPROST (CLINICAL TRIALS)		
MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Eye disorders	Very common	Eye irritation (burning, grittiness, itching, stinging and foreign body sensation)
	Common	Eyelid oedema; transient punctate epithelial erosions
Skin and subcutaneous tissue disorders	Common	Skin rash
LATANOPROST: POST-MARKETING SURVEILLANCE		
MedDRA System Organ Class	**Undesirable Effects**	
Nervous system disorders	Dizziness	
Eye disorders	Eyelash and vellus hair changes (increased length, thickness, pigmentation, and number), vision blurred, iritis/uveitis, macular oedema including cystoid macular oedema, corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation	
Respiratory, thoracic and mediastinal disorders	Asthma, dyspnoea, asthma aggravation, acute asthma attacks	
Skin and subcutaneous tissue disorders	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	

TIMOLOL MALEATE (OCULAR ADMINISTRATION)	
MedDRA **System Organ Class**	**Undesirable effects**
Immune system disorders	Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localised and generalised rash
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
Nervous system disorders	Dizziness, paraesthesia, somnolence, cerebral ischaemia, cerebral vascular accident, increase in signs and symptoms of myasthenia gravis, syncope
Eye disorders	Visual disturbance including refractive changes and diplopia, ptosis, cystoid macular oedema, decreased corneal sensitivity, choroidal detachment following filtration surgery
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Dysrhythmia, bradycardia, palpitation, cardiac arrest, cardiac failure, heart block, 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
Skin and subcutaneous tissue disorders	Alopecia pseudopemphigoid, psoriasiform rash or exacerbation of psoriasis

Musculoskeletal and connective tissue disorders	Systemic lupus erythematosus
Reproductive system and breast disorders	Impotence, Peyronie's disease
General disorders and administration site conditions	Asthenia/fatigue, chest pain, oedema

Special precautions:

Ocular effects:

Latanoprost may gradually change the eye colour by increasing the amount of brown pigment in the iris. 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 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.

There is no documented experience with latanoprost-timolol in inflammatory, neovascular, chronic angle closure or congenital glaucoma, in open angle glaucoma of pseudophakic patients and in pigmentary glaucoma.

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. XALACOM should be used with caution in these patients.

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

Systemic effects:

XALACOM may be absorbed systemically. Due to the beta-adrenergic component timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-blockers may occur.

In patients with cardiovascular diseases (e.g. coronary heart disease, sick sinus syndrome, peripheral circulatory disturbances – hypotension, Prinzmetal's angina, cardiac failure) the 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.

Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failures, have been reported following administration of timolol.

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

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 unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Use of contact lenses:

XALACOM contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy, may cause eye irritation and is known to discolour soft contact lenses. Close

monitoring is required with frequent or prolonged use of XALACOM 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 XALACOM but may be reinserted after 15 minutes.

Concomitant therapy:

The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when XALACOM is given to patients already receiving an oral beta-blocking agent. The use of two local beta-blockers or two local prostaglandins is not recommended.

Timolol may interact with other medicines, see INTERACTIONS.

Effects 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Apart from ocular irritation and conjunctival hyperaemia, no other ocular or systemic side effects are known if latanoprost is overdosed. Symptoms of systemic timolol overdosage are bradycardia, hypotension, bronchospasm and cardiac arrest.

If such symptoms occur, the treatment should be symptomatic and supportive.

If latanoprost is accidentally ingested, the following may be useful: One 2,5 ml bottle contains 125 micrograms latanoprost. More than 90 % is metabolised during the first pass through the liver. Intravenous infusion of 3 µg/kg in healthy volunteers induced no symptoms, but a dose of 5,5 – 10 µg/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. In patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost such as included in XALACOM when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost. Studies have shown that timolol does not dialyse readily.

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

IDENTIFICATION:

A clear and colourless solution, free of visible particles.

PRESENTATION:

The drops are available in a 5 ml multidose, clear, colourless, low-density polyethylene bottle, with a clear, linear, low-or medium-density polyethylene dropper tip (applicator), protected with a yellow inner high-density polyethylene screw cap, and a clear, colourless tamper-evident overcap of low-density polyethylene.

Each bottle contains 2,5 ml eye drop solution.

STORAGE INSTRUCTIONS:

Store in a refrigerator (2 °C – 8 °C) in the original carton. Once the bottle is opened the contents must be used within 30 days and may be stored at room temperature up to 25 °C. After opening, the bottle must be stored in the carton to protect it from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

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NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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