XALACOM® EYE DROPS

1. NAME OF THE MEDICINAL PRODUCT

Xalacom® eye drops.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1mL solution contains latanoprost 50 micrograms and timolol maleate 6.8 mg equivalent to 5 mg timolol.

Excipients with known effect: Benzalkonium chloride 0.2 mg /ml

Disodium phosphate, sodium dihydrogen phosphate monohydrate (containing total phosphate 6.3 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 PARTICULARS

4.1. Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who are insufficiently responsive to topical beta-blockers.

4.2. Posology and method of administration

Posology

Adults (including the elderly)
Recommended therapy is one eye drop in the affected eye(s) once daily.

If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the effected eye(s) daily, since it has been shown that more frequent administration of latanoprost decreases the intraocular pressure lowering effect.

Paediatric population
The safety and efficacy of Xalacom eye drops in children below 18 years of age has not been established.

Method of administration
Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes. (see section 4.4)

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3. Contraindications

Xalacom is contraindicated in patients with:

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

4.4. Special warnings and precautions for use

Systemic effects

Like other topically applied ophthalmic agents, Xalacom 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 agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders

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

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

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

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. Xalacom should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycemia/diabetes

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

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases

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

Other beta-blocking agents

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5).

Anaphylactic reactions

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

Choroidal detachment

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

Surgical anaesthesia

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

Concomitant therapy

Timolol may interact with other drugs see section 4.5.

Other prostaglandin analogues

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

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, increased iris pigmentation was seen in16-20% of all patients treated with Xalacom for up to one year (based on photographs). 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. In patients with homogeneously blue, grey, green or brown eyes, the change has only rarely been seen during two years of treatment in clinical trials with latanoprost.

The change in iris colour occurs slowly and may not be noticeable for several months to years and it has not been associated with any symptom or pathological changes.

No further increase in brown iris pigment has been observed after discontinuation of treatment, but the resultant colour change may be permanent.

Neither naevi nor freckles of the iris have been affected by the treatment.

Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed but patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased iris pigmentation ensues.

Before treatment is instituted patients should be informed of the possibility of a change in eye colour. Unilateral treatment can result in permanent heterochromia.

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 Xalacom 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. Xalacom should be used with caution in these patients.

Preservative
Xalacom contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride has been reported to cause punctuate keratopathy and/or toxic ulcerative keratopathy and may cause eye irritation. 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

Contact lenses may absorb benzalkonium chloride which is known to discolour soft contact lenses. Contact lenses should be removed before applying Xalacom but may be reinserted after 15 minutes (see section 4.2).

4.5. Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with Xalacom.

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 beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

Potentiated systemic beta blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

The effect on intraocular pressure or the known effects of systemic 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.

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 agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).

4.6. Fertility, pregnancy and lactation

Pregnancy

Latanoprost

There are no adequate data from the use of latanoprost in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). 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 unless clearly necessary. To reduce the systemic absorption, see section 4.2.

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 beta-blockers have been administered until delivery. If Xalacom is administered until delivery, the neonate should be carefully monitored during the first days of life.

Consequently, Xalacom should not be used during pregnancy (see section 5.3).

Breast-feeding

Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

Latanoprost and its metabolites may pass into breast milk. Xalacom should therefore not be used in women who are breast-feeding

Fertility

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

4.7. Effects on ability to drive and use machines

Xalacom 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

For latanoprost, the majority of adverse reactions relate to the ocular system. In data from the extension phase of the Xalacom pivotal trials, 16 - 20% of patients developed increased iris pigmentation, which may be permanent. In an open 5 year latanoprost safety study, 33% of patients developed iris pigmentation (see section 4.4). Other ocular adverse reactions are generally transient and occur on dose administration. For timolol, the most serious adverse reactions are systemic in nature, including bradycardia, arrhythmia, congestive heart failure, bronchospasm and allergic reactions.

Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

Treatment related adverse reactions seen in clinical trials with Xalacom are listed below.

Adverse reactions are categorized by frequency as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to<1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000), not known (frequency cannot be estimated from the available data).

Table 1: Adverse reactions seen in Xalacom trials

System Organ Class	**Very common (≥1/10)**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**
Nervous system disorders			Headache
Eye disorders	Iris hyperpigmentation	Eye pain, eye irritation (including stinging, burning, itching, foreign body sensation)	Corneal disorders, conjunctivitis, blepharitis, eye hyperaemia, vision blurred, lacrimation increased
Skin and subcutaneous tissue disorders			Rash, pruritus

Additional adverse reactions have been reported specific to the use of the individual components of Xalacom in either clinical studies, spontaneous reports or in the available literature.

For latanoprost, these are:

Table 2: Adverse Reaction for Latanoprost

System Organ Class	**Adverse Reactions**
Infections and infestations	Herpetic keratitis

Table 2: Adverse Reaction for Latanoprost

System Organ Class	Adverse Reactions
Nervous system disorders	Dizziness
Eye disorders	Eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes); punctate keratitis, periorbital oedema; iritis; uveitis; macular oedema including cystoid macular oedema; dry eye; keratitis; corneal oedema; corneal erosion; trichiasis; iris cyst; photophobia; periorbital and lid changes resulting in deepening of the eyelid sulcus; eyelid oedema; localised skin reaction on the eyelids; pseudopemphigoid of the ocular conjunctiva[+]; darkening of the palpebral skin
Cardiac disorders	Angina; angina unstable; palpitations
Respiratory, thoracic and mediastinal disorders	Asthma; asthma aggravation; dyspnoea
Gastrointestinal disorders	Nausea*; vomiting*
Musculoskeletal and connective tissue disorders	Myalgia; arthralgia
General disorders and administration site conditions	Chest pain

*Identified post marketing with an estimated frequency of uncommon
[+] May be potentially related to the preservative benzalkonium chloride

For timolol, these are:

Table 3: Adverse Reaction for Timolol Maleate (ocular administration)

System Organ Class	Adverse Reactions
Immune system disorders	Systemic allergic reactions including anaphylactic reaction, angioedema, urticaria, localised and generalised rash, pruritus
Metabolism and nutrition disorders	Hypoglycaemia
Psychiatric disorders	Memory loss, insomnia, depression, nightmares, hallucinations
Nervous system disorders	Cerebrovascular accident, cerebral ischaemia, dizziness, increases in signs and symptoms of myasthenia gravis, paraesthesia, headache, syncope
Eye disorders	Choroidal detachment following filtration surgery (see section 4.4), corneal erosion, keratitis, diplopia, decreased corneal sensitivity, signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing and redness), dry eyes, ptosis, blepharitis, blurred vision
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Cardiac arrest, cardiac failure, atrioventricular block, congestive heart failure, chest pain, arrhythmia, bradycardia, oedema, palpitations
Vascular disorders	Cold hands and feet, hypotension, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Bronchospasm (predominately in patients with pre-existing bronchospastic disease), cough, dyspnoea
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea, dry mouth,

Table 3: Adverse Reaction for Timolol Maleate (ocular administration)

System Organ Class	Adverse Reactions
	dysgeusia, dyspepsia, nausea
Skin and subcutaneous tissue disorders	Skin rash, psoriasiform rash, exacerbation of psoriasis, alopecia
Musculoskeletal and connective tissue disorders	Myalgia
Reproductive system and breast disorders	Sexual dysfunction, decreased libido
General disorders and administration site conditions	Asthenia, fatigue

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9. Overdose

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

Symptoms

Symptoms of systemic timolol overdose are: 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.

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. Gastric lavage if needed. Latanoprost is extensively metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers induced no symptoms, but a dose of 5.5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating. These events were mild to moderate in severity and resolved without treatment, within 4 hours after terminating the infusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Ophthalmological – betablocking agents – timolol, combinations
ATC code: S01ED51

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 and the combined effect results in additional IOP reduction compared to either compound administered alone.

Latanoprost, a prostaglandin $F_{2\alpha}$ analogue, is a selective prostanoid FP receptor agonist that reduces the IOP by increasing the outflow of aqueous humour. The main mechanism of action is increased uveoscleral outflow. Additionally, some increase in outflow facility (decrease in trabecular outflow resistance) has been reported in man. Latanoprost has no significant effect on the production of aqueous humour, the blood-aqueous barrier or the intraocular blood circulation. Chronic treatment with latanoprost in monkey eyes, which had undergone extracapsular lens extraction did not affect the retinal blood vessels as determined by fluorescein angiography. Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short term treatment.
Timolol is a beta-1 and beta-2 (non-selective) adrenergic receptor blocking agent that has no significant intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Timolol lowers IOP by decreasing the formation of aqueous in the ciliary epithelium.
The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable. Timolol has not been found to significantly affect the permeability of the blood-aqueous barrier to plasma proteins. In rabbits, timolol was without effect on the regional ocular blood flow after chronic treatment.

Pharmacodynamic effects

Clinical efficacy and safety

In dose finding studies, Xalacom produced significantly greater decreases in mean diurnal IOP compared to latanoprost and timolol administered once daily as monotherapy. In two well controlled, double masked six-month clinical studies the IOP reducing effect of Xalacom was compared with latanoprost and timolol monotherapy in patients with an IOP of at least 25 mm Hg or greater. Following a 2-4 week run-in with timolol (mean decrease in IOP from enrollment of 5 mm Hg), additional decreases in mean diurnal IOP of 3.1, 2.0 and 0.6 mm Hg were observed after 6 months of treatment for Xalacom, latanoprost and timolol (twice daily), respectively. The IOP lowering effect of Xalacom was maintained in 6 month open label extension of these studies.

Existing data suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, when considering a recommendation of either morning or evening dosing, sufficient consideration should be given to the lifestyle of the patient and their likely compliance.

It should be kept in mind that in case of insufficient efficacy of the fixed combination, results from studies indicate that the use of unfixed administration of Timolol bid and latanoprost once a day might be still efficient.

Onset of action of Xalacom is within one hour and maximal effect occurs within six to eight hours. Adequate 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, which per se is inactive but after hydrolysis by esterases in the cornea to the acid of latanoprost, becomes biologically active. The prodrug is well absorbed through the cornea and all drug that enters the aqueous humor is hydrolysed during the passage through the cornea.

Distribution
Studies in man indicate that the maximum concentration in the aqueous humour, approximately 15-30 ng/mL, is reached about 2 hours after topical administration of latanoprost alone.After topical application in monkeys latanoprost is distributed primarily in the anterior segment, the conjunctiva and the eye lids.

The acid of latanoprost has a plasma clearance of 0.40 l/h/kg and a small volume of distribution, 0.16 l/kg, resulting in a rapid half life in plasma, 17 minutes. After topical ocular administration the systemic bioavailability of the acid of latanoprost is 45%. The acid of latanoprost has a plasma protein binding of 87%.

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 and are excreted primarily in the urine.

Timolol

Absorption and distribution
The maximum concentration of timolol in the aqueous humour is reached about 1 hour after topical administration of eye drops. Part of the dose is absorbed systemically and a maximum plasma concentration of 1 ng/mL is reached 10-20 minutes after topical administration of one eye drop to each eye once daily (300 micrograms/day).

Biotransformation
The half life of timolol in plasma is about 6 hours. Timolol is extensively metabolised in the liver.

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

Xalacom

Pharmacokinetic/pharmacodynamic relationship
No pharmacokinetic interactions between latanoprost and timolol were observed, although there was an approximate 2-fold increased concentration of the acid of latanoprost in aqueous humour 1-4 hours after administration of Xalacom compared to monotherapy.

5.3. Preclinical safety data

The ocular and systemic safety profile of the individual components is well established. No adverse ocular or systemic effects were seen in rabbits treated topically with the fixed combination or with concomitantly administered latanoprost and timolol ophthalmic solutions. Safety pharmacology, genotoxicity and carcinogenicity studies with each of the components revealed no special hazards for humans. Latanoprost did not affect corneal wound healing in the rabbit eye, whereas timolol inhibited the process in the rabbit and the monkey eye when administered more frequently than once a day.

For latanoprost, no effects on male and female fertility in rats and no teratogenic potential in rats and rabbits have been established. No embryotoxicity was observed in rats after intravenous doses of up to 250 micrograms/kg/day. However, latanoprost caused embryofetal toxicity, characterised by increased incidence of late resorption and abortion and by reduced foetal weight, in rabbits at intravenous doses of 5 micrograms/kg/day (approximately 100 times the clinical dose) and above.
Timolol showed no effects on male and female fertility in rats or teratogenic potential in mice, rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium dihydrogen phosphate monohydrate
Sodium chloride
Disodium phosphate anhydrous
Benzalkonium chloride
Water for injections

6.2. Incompatibilities

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

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

After opening of container: 4 weeks

6.4. Special precautions for storage

Before first opening: Store in a refrigerator (2°C – 8°C)

After first opening: Store below 25°C.

Use within 4 weeks (see section 6.3).

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

6.5. Nature and content of container

Bottle (5ml) of polyethylene and dropper applicator (dropper tip) with HDPE screw cap and tamper evident polyethylene overcap.

Each bottle contains 2.5 mL eye drop solution.

6.6. Instructions for use and handling

The tamper evident overcap should be removed before use.

7. LICENSE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd. 9 Shenkar St., Herzliya Pituach, 46725, Israel.

8. LICENSE NUMBER

124-62-30356

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