Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Xalacom 50 micrograms/ml + 5 mg/ml Eye Drops, Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient: Contains benzalkonium chloride
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Eye Drops, Solution

Product imported from Greece:
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 or prostaglandin analogues.

4.2 Posology and method of administration

Recommended dosage for 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 affected eye(s) daily.

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.

Use in children and adolescents:
Safety and effectiveness in children and adolescents has not been established.

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, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock.
- Hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and precautions for use

Systemic effects

Like other topically applied ophthalmic agents, 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, 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 maleate.

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.

Concomitant therapy:

Timolol may interact with other drugs see 4.5 Interaction with other medicinal products and other forms of interaction.

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.

Ocular effects:

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 Xalcom 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 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.

There is no documented experience with latanoprost in inflammatory, neovascular, chronic angle closure or congenital 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.

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.

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 punctuate 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 (see section 4.2 Posology and Method of Administration).

4.5 Interaction with other medicinal products and other forms of interaction

Specific medicinal product interaction studies have not 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.

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 has occasionally been reported when timolol was given with epinephrine.

There is a potential for additive effects resulting in hypotension, and/or marked bradycardia when eye drops with timolol are administered concomitantly with oral calcium channel blockers, guanethidine or beta-blocking agents, antiarrythmics, digitalis glycosides or parasympathomimetics.

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 4.4 Special warnings and special precutions for use).*

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 5.3).* The potential risk for humans is unknown.

Timolol:
Well controlled epidemiological studies with systemic use of beta-blockers did not indicate malformative effects, but some pharmacological effects such as bradycardia have already been observed in foetuses or neonates.

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

Lactation

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

4.7 Effects on 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 events 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 4.4).* Other ocular adverse events are generally transient and occur on dose administration. For timolol, the most serious adverse events are systemic in nature, including bradycardia, arrhythmia, congestive heart failure, bronchospam and allergic reactions.

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

Adverse events are categorized by frequency as follows: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,0000, <1/1000) and very rare (<1/10,000).

Nervous System Disorders	
Uncommon:	Headache.
Eye Disorders	
Very common:	Increased iris pigmentation.
Common:	Eye irritation (including stinging, burning and itching), Eye pain
Uncommon:	Eye hyperaemia, Conjunctivitis, Vision blurred, Lacrimation increased, Blepharitis, Corneal disorders
Skin and Subcutaneous Tissue Disorders	
Uncommon:	Skin rash, Pruritus

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

For latanoprost, these are:

Nervous System Disorders:
Dizziness.

Eye Disorders:
Eyelash and vellus hair changes (increased length, thickness, pigmentation, and number), Punctate epithelial erosions, periorbital oedema, iritis/uveitis, macular oedema (in aphakic, pseudophakic patients with torn posterior lens capsules or in patients with known risk factors for macular oedema). Dry eye, keratitis, corneal oedema and erosions, misdirected eyelashes sometimes resulting in eye irritation and iris cyst.

Cardiac Disorders:
Aggravation of angina in patients with pre-existing disease, Palpitations.

Respiratory, Thoracic and Mediastinal Disorders:
Asthma, asthma aggravation, dyspnoea

Skin and Subcutaneous Tissue Disorders:
Darkening of palpebral skin.

Musculoskeletal and Connective Tissue Disorders:
Join pain, muscle pain.

General disorders and Administration Site Conditions:
Chest pain

For timolol, these are:

Immune System Disorders:
Signs and symptoms of systemic allergic reactions including angioedema, urticaria, and localized and generalized rash.

Psychiatric Disorders:
Depression, memory loss, decreased libido, insomnia, nightmares.

Nervous System Disorders:
Dizziness, paresthesia, . cerebral ischaemia, cerebrovascular accident, increase in signs and symptoms of myasthenia gravis, syncope.

Eye Disorders:
Signs and symptoms of ocular irritation including keratitis, decreased corneal sensitivity and dry eyes, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis, choroidal detachment (following filtration surgery).

Ear and Labyrinth Disorders:
Tinnitus.

Cardiac Disorders:
Palpitation, arrhythmia, bradycardia, cardiac arrest, heart block, congestive heart failure.

Vascular Disorders:
Hypotension, Raynaud’s phenomenon, cold hands and feet.

Respiratory, Thoracic and Mediastinal Disorders:
Bronchospasm (predominately in patients with pre-existing bronchospastic disease), dyspnoea, cough.

Gastrointestinal Disorders:
Nausea, diarrhoea, dyspepsia, dry mouth.

Skin and Subcutaneous Tissue Disorders:
Alopecia, psoriasiform rash or exacerbation of psoriasis.

General disorders and administration site conditions:
Asthenia/fatigue, chest pain, oedema.

4.9 Overdose

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

Symptoms of systemic timolol overdose are: bradycardia, hypotension, bronchospasm and cardiac arrest. If such symptoms occur the treatment should be symptomatic and supportive. Studies have shown that timolol does not dialyse readily.

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

If latanoprost is accidentally ingested orally the following information may be useful:

Treatment: Gastric lavage if needed. Symptomatic treatment. 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_{2alpha} 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 effects
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
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. 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%.

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 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). The half life of timolol in plasma is about 6 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 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 chloride
Benzalkonium chloride
Sodium dihydrogen phosphate monohydrate
Disodium phosphate anhydrous
Hydrochloric acid solution (for adjustment to pH 6.0)
Sodium hydroxide solution (for adjustment to pH 6.0)
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 shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

After opening of container: 4 weeks

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Opened bottle: Do not store above 25 °C.

Keep the bottle in the outer carton

6.5 Nature and contents of container

LDPE bottle (5 ml) and dropper applicator (dropper tip), HDPE screw cap, tamper evident LDPE overcap.

Each bottle contains 2.5 ml eye drop solution.

Pack size: 1 x 2.5 ml

6.6 Special precautions for disposal and other handling

The tamper evident overcap should be removed before use.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing Limited,
Unit 10, Ashbourne Business Park,
Rath,
Ashbourne,
Co. Meath.

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA465/269/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th April 2011

10 DATE OF REVISION OF THE TEXT