

AUSTRALIAN PRODUCT INFORMATION – XALACOM[®] (LATANOPROST AND TIMOLOL MALEATE) EYE DROPS

1. NAME OF THE MEDICINE

Latanoprost and timolol maleate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Xalacom is a combination eye drop containing latanoprost and timolol maleate.

Latanoprost is a prostaglandin F_{2α} analogue.

Xalacom is a sterile, isotonic solution containing 50 micrograms/mL of latanoprost and 5 mg/mL of timolol (6.83 mg timolol maleate) in an aqueous buffer solution of pH 6.0.

Each 5 mL bottle contains 2.5 mL eye drop solution corresponding to a minimum of 80 drops of solution. One drop contains approximately 1.5 µg latanoprost and 150 µg timolol.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Eye drops, solution.

The solution is a clear and colourless liquid, filled in a polyethylene container.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are insufficiently responsive to beta-blockers, prostaglandins or other intraocular pressure lowering medications. Xalacom should not be used to initiate therapy.

4.2 Dose and method of administration

Dosage

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 normal.

The use of Xalacom may be considered in patients who require both timolol and latanoprost, but it is unknown whether patients who are adequately controlled with timolol given twice

daily plus latanoprost given once daily will be as well controlled with Xalacom given once daily. Xalacom should not be used to initiate therapy.

Xalacom should not be given more than once daily because latanoprost is most effective at this dosage. If there is inadequate response to Xalacom, consideration should be given to using the individual agents with timolol dose twice daily.

Method of Administration

If more than one topical ophthalmic drug is being used, the eye drop products should be administered at least 5 minutes apart.

Systemic absorption can be minimised by pressure on the tear duct immediately after application of the eye drop.

Use with contact lenses: The contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes (see Section 4.4 Special warnings and precautions for use).

4.3 Contraindications

Xalacom is contraindicated in patients with:

- reactive airway disease including bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease.
- sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock.
- known hypersensitivity to latanoprost, timolol maleate or any of the excipients in Xalacom.

4.4 Special warnings and precautions for use

Systemic Effects

Cardiovascular/respiratory reactions

Like other topically applied ophthalmic agents, Xalacom may be absorbed systemically. Due to the beta-adrenergic component timolol, the same types of adverse reactions seen with systemic beta-blockers may occur including aggravation of Prinzmetal's angina, aggravation of severe peripheral and central circulatory disorders, bradycardia and hypotension.

Respiratory and cardiac reactions, including death due to bronchospasm in patients with asthma and, death associated with cardiac failure have been reported following administration of timolol. Cardiac failure should be adequately controlled before treatment. Patients with a history of severe cardiac disease should be monitored closely for signs of cardiac failure.

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

Patients with severe peripheral circulatory disturbance/disorders (i.e., severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Timolol maleate 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.

A gradual withdrawal of beta-adrenergic blocking agents prior to major surgery may 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-blocking ophthalmological preparations may block systemic beta-agonist effects e.g., of adrenaline. The anaesthetist should be informed when the patient is receiving timolol.

Hypersensitivity 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, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Concomitant therapy

Timolol may interact with other drugs (see Section 4.5 Interactions with other medicines and other forms of interactions).

The effect on intraocular pressure or the known effects of systemic beta-blockade may be exaggerated when Xalacom is given to patients already receiving an oral beta-blocking agent. There have been reports of paradoxical elevations in IOP following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more local beta-blockers or two or more local prostaglandins, prostaglandin analogues, or prostaglandin derivatives is not recommended.

Hypoglycaemia

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycaemic agents. Beta-blockers may increase the hypoglycaemic effect of agents used to treat diabetes and may mask the signs and symptoms of acute hypoglycaemia.

Hyperthyroidism

Therapy with beta-blockers may mask certain signs and symptoms of hyperthyroidism and abrupt withdrawal of therapy may precipitate a worsening of symptoms.

Myasthenia gravis

Therapy with beta-blockers may aggravate symptoms of myasthenia gravis.

Ocular Effects

Iris pigmentation changes

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. 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 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 or limited experience with latanoprost or latanoprost-timolol 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 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.

Choroidal detachment and corneal disease

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

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

Use of Contact Lenses

Xalacom contains benzalkonium chloride which may be absorbed by contact lenses. Several contact lens soaking solutions contain thiomersal which may also form a precipitate with the benzalkonium chloride (see Section 4.5 Interactions with other medicines and other forms of interactions). Therefore contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.

Use in the Elderly

No data available.

Paediatric Use

Xalacom is not recommended for use in children. Safety and effectiveness in children have not been established.

Effects on Laboratory Tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

No specific interaction studies have been performed with Xalacom.

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

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.

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 antidiabetic agents (see Section 4.4 Special warnings and precautions for use - Hypoglycaemia).

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with benzalkonium chloride, the preservative used in Xalacom. If such drugs are used they should be administered with an interval of at least five (5) minutes between applications. Similarly several contact lens soaking solutions contain thiomersal (see Section 4.4 Special warnings and precautions for use - Use of Contact Lenses).

4.6 Fertility, pregnancy and lactation

Effects on Fertility

Fertility studies with Xalacom have not been conducted. Latanoprost or timolol maleate alone had no effects on male or female fertility in rats when administered at 250 µg/kg/day IV or 300 mg/kg/day PO respectively.

Use in Pregnancy – Category C

Embryofetal development studies with latanoprost have been performed in rats and rabbits. Latanoprost and/or its metabolites cross the placenta of rats. In rabbits, latanoprost caused embryofetal toxicity characterised by increased incidences of late resorption and reduced fetal weight at 5 µg/kg/day IV and total litter resorption at ≥ 50 µg/kg/day IV. No embryofetal effects were seen in rabbits at 1 µg/kg/day IV and in rats at up to 250 µg/kg/day IV.

Timolol maleate was not teratogenic in mice, rats and rabbits. Embryofetal development studies with timolol maleate in mice and rabbits showed no evidence of embryofetal toxicity at oral doses up to 50 mg/kg/day. At higher doses, increases in resorptions and fetal variations (14 ribs and hypoplastic sternebrae) were noted in mice (1000 mg/kg/day) and increased resorption in rabbits (≥ 90 mg/kg/day). In rats, delayed ossification was seen at ≥ 50 mg/kg/day and a decreased number of caudal vertebral bodies and arches and an increase in hypoplastic sternebrae were noted at 500 mg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Therefore, Xalacom should not be used during pregnancy.

Use in Lactation

There are limited experimental animal and no human data available on the pharmacokinetics of latanoprost in lactation. Latanoprost and its metabolites may pass into breast milk.

Timolol maleate has been detected in human milk following oral and ocular administration. Because of the potential for serious adverse reactions from Xalacom in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on 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 Adverse effects (undesirable effects)

No adverse events specific for Xalacom have been observed in clinical studies. The adverse events have been limited to those earlier reported for latanoprost and timolol.

Adverse Events from Clinical Trials

Adverse events occurring at a frequency of $\geq 1\%$ in three randomised, double blind comparative trials (004, 005 and 053) are presented in Tables 1 and 2.

Table 1: Ocular adverse events (AE) that occurred in $\geq 1\%$ of patients*, in any treatment group, by preferred term†

Body system / preferred term	Number (%) of patients per treatment group		
	Xalacom N=394	Latanoprost N=414	Timolol N=415
Eye disorders			
Blepharitis	10 (2.5)	10 (2.4)	7 (1.7)
Cataract	11 (2.8)	18 (4.3)	10 (2.4)
Conjunctival disorder	4 (1.0)	3 (0.7)	4 (1.0)
Conjunctivitis	12 (3.0)	11 (2.7)	13 (3.1)
Corneal disorder	12 (3.0)	11 (2.7)	14 (3.4)
Corneal ulceration	1 (0.3)*	1 (0.2)*	-
Cystoid macular oedema	1 (0.3)*	1 (0.2)*	-
Epiphora	3 (0.8)	5 (1.2)	7 (1.7)
Errors of refraction	7 (1.8)	13 (3.1)	12 (2.9)
Eye hyperaemia	29 (7.4)	40 (9.7)	12 (2.9)
Eye pain	9 (2.3)	6 (1.4)	8 (1.9)
Increased intraocular pressure	1 (0.3)	5 (1.2)	7 (1.7)
Iris hyperpigmentation	6 (1.5)	13 (3.1)	4 (1.0)
Iritis	-	1 (0.2)*	2 (0.5)*
Irritation eye	49 (12.4)	54 (13.0)	29 (7.0)
Keratitis	4 (1.0)	3 (0.7)	1 (0.2)
Oedema eyelid	2 (0.5)	4 (1.0)	2 (0.5)
Photophobia	6 (1.5)	1 (0.2)	3 (0.7)
Retinal disorder	1 (0.3)	3 (0.7)	6 (1.4)
Uveitis	1 (0.3)*	-	-
Vision abnormal	26 (6.6)	29 (7.0)	22 (5.3)
Optic atrophy	2 (0.5)	3 (0.7)	6 (1.4)
Skin and subcutaneous tissue disorders			
Hypertrichosis‡	9 (2.3)	6 (1.4)	2 (0.5)
Pigmentation abnormal	1 (0.3)*	-	-
Seborrhoea	2 (0.5)	4 (1.0)	-
Skin discolouration	1 (0.3)*	-	-
Skin disorder	8 (2.0)	4 (1.0)	-
Nervous system disorders			
Visual field defect	18 (4.6)	19 (4.6)	18 (4.3)

* Despite a low frequency of reports, some AEs are included in the listing due to the implication of a potentially sight-threatening condition.

A patient is counted only once per preferred term.

† Studies 004 and 005 included a 6 month and 053 a 12 month double-blinded period.

‡ Includes darkening, lengthening and growing of eye lashes.

Table 2: Systemic adverse events (AE) that occurred in ≥1% of patients*, in any of the treatment groups, by body system/preferred term†

Body system / preferred term	Number (%) of patients per treatment group		
	Xalacom N=394	Latanoprost N=414	Timolol N=415
Respiratory, thoracic and mediastinal disorders			
Bronchitis	3 (0.8)	4 (1.0)	1 (0.2)
Coughing	1 (0.3)*	-	2 (0.5)*
Dyspnoea	2 (0.5)*	2 (0.5)*	2 (0.5)*
Pneumonia	1 (0.3)	3 (0.7)	4 (1.0)
Sinusitis	6 (1.5)	11 (2.7)	3 (0.7)
Upper respiratory tract infection	24 (6.1)	18 (4.3)	22 (5.3)
General disorders and administration site conditions			
Back pain	4 (1.0)	6 (1.4)	4 (1.0)
Chest pain	4 (1.0)	1 (0.2)	2 (0.5)
Influenza-like symptoms	10 (2.5)	4 (1.0)	3 (0.7)
Vascular disorders			
Hypertension	15 (3.8)	6 (1.4)	10 (2.4)
Hypertension aggravated	2 (0.5)*	1 (0.2)*	1 (0.2)*
Metabolic and nutrition disorders			
Diabetes mellitus	5 (1.3)	2 (0.5)	1 (0.2)
Diabetes mellitus aggravated	-	1 (0.2)	-
Glycosuria	2 (0.5)	1 (0.2)	-
Hyperglycaemia	1 (0.3)*	2 (0.5)*	2 (0.5)*
Hypercholesterolaemia	6 (1.5)	4 (1.0)	1 (0.2)
Nervous system disorders			
Dizziness	2 (0.5)	4 (1.0)	1 (0.2)
Headache	9 (2.3)	15 (3.6)	5 (1.2)
Musculoskeletal and connective tissue disorders			
Arthritis	8 (2.0)	5 (1.2)	4 (1.0)
Psychiatric disorders			
Depression	6 (1.5)	7 (1.7)	4 (1.0)
Insomnia	1 (0.3)*	1 (0.2)*	1 (0.2)*
Sleep disorder	1 (0.3)	-	4 (1.0)
Skin and subcutaneous tissue disorders			
Bullous eruption	-	1 (0.2)	-
Rash	5 (1.3)	3 (0.7)	2 (0.5)
Infections and infestation			
Infection	4 (1.0)	6 (1.4)	6 (1.4)
Gastrointestinal disorders			
Dyspepsia	2 (0.5)	4 (1.0)	1 (0.2)
Renal and urinary disorders			
Cystitis	1 (0.3)	5 (1.2)	-

Body system / preferred term	Number (%) of patients per treatment group		
	Xalacom N=394	Latanoprost N=414	Timolol N=415
Urinary tract infection	1 (0.3)	2 (0.5)	4 (1.0)

* A patient is counted only once per preferred term. AEs that occurred in <1 % of the patients but were very similar to an event that did occur in ≥1% of the patients (such as “hypertension” and “hypertension aggravated”) are listed. Also, groups of mutually related AEs, where each AE may be reported in < 1%, but together they sum up to ≥1% (such as “diabetes mellitus aggravated” and “hyperglycaemia” together with “glucosuria”) are summarised.

† Studies 004 and 005 included a 6 month- and 053 a 12 month double-blinded period.

The following additional adverse events have been reported with the single component latanoprost

Eye disorder: Eye irritation (burning, grittiness, itching, stinging, tearing, redness and foreign body sensation), punctate keratitis, macular oedema, corneal oedema, corneal erosions, eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes), trichiasis, blurred vision, periorbital and lid changes resulting in deepening of the eyelid sulcus, darkening of the palpebral skin of the eyelids, localised skin reaction on the eyelids.

Respiratory, thoracic and mediastinal disorders: Asthma, asthma aggravation and acute asthma attacks.

Musculoskeletal and connective tissue disorders: Myalgia, arthralgia.

General disorders and administration site conditions: Chest pain.

Infections and infestations: Herpetic keratitis.

The following additional adverse events have been reported with the single component timolol by ocular administration:

Eye disorders: Visual disturbances including refractive changes, hypoaesthesia eye, signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing, redness), vision blurred, dry eyes, corneal erosion, diplopia, ptosis, choroidal detachment (following filtration surgery).

Ear and labyrinth disorders: Tinnitus.

Cardiac disorders: Bradycardia, arrhythmia, atrioventricular block, hypotension, heart block, congestive heart failure, palpitation, cardiac arrest, cardiac failure, worsening of angina pectoris.

Vascular disorders: Claudication, cold hands and feet, hypotension, Raynaud’s phenomenon.

Respiratory, thoracic and mediastinal disorders: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, pulmonary oedema and nasal congestion.

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

Skin and subcutaneous tissue disorders: Alopecia, pseudopemphigoid, psoriasiform rash or exacerbation of psoriasis.

Immune system disorders: Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, pruritus, localised and generalised rash.

Nervous system disorders: Cerebral vascular accident, cerebral ischaemia, increase in signs and symptoms of myasthenia gravis, paraesthesia, somnolence, headache, syncope.

Psychiatric disorders: Nightmares, behavioural changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness and memory loss.

Gastrointestinal disorders: Nausea, diarrhoea, dry mouth, dysgeusia, vomiting, abdominal pain, retroperitoneal fibrosis.

Metabolism and nutrition disorders: Anorexia, masked symptoms of hypoglycaemia in diabetic patients.

Musculoskeletal and connective tissue disorders: Myalgia, systemic lupus erythematosus.

Reproductive system and breast disorders: Decreased libido, Peyronie's disease, sexual dysfunction, impotence.

Post-marketing Experience

The following additional adverse drug reactions have been observed post-marketing with the single component latanoprost and may also be relevant for the latanoprost and timolol combination.

Eye disorders: Iris cyst, pseudopemphigoid of the ocular conjunctiva.

Cardiac disorders: Unstable angina, angina, palpitations.

Skin and subcutaneous tissue disorders: Pruritus.

Adverse reactions reported with the use of eye drops containing phosphate buffers.

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 Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms

There is no human data available on overdosage with Xalacom.

There have been reports of inadvertent overdosage with timolol-maleate ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, hypotension, bronchospasm, and cardiac arrest. Apart from ocular irritation and conjunctival or episcleral hyperaemia, the ocular effects of latanoprost administered at high doses are not known.

Treatment

If overdosage with Xalacom occurs, treatment should be symptomatic and supportive. Studies have shown that timolol is not readily dialyzable. If Xalacom is accidentally ingested the following information may be useful: One bottle contains 125 µg latanoprost and 12.5 mg timolol. Both timolol and latanoprost are extensively metabolised in the liver. More than 90% of latanoprost is metabolised during the first pass through the liver. Intravenous infusion of up to 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. These events were mild to moderate in severity and resolved without treatment within 4 hours after terminating the infusion. In patients with bronchial asthma bronchoconstriction was not induced by latanoprost when applied topically on the eyes in a dose of seven times the clinical dose of latanoprost.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

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

Latanoprost

Latanoprost is a selective prostanoid F_{2α} receptor agonist which reduces IOP by increasing the outflow of aqueous humour. The main mechanism of action is increased uveoscleral outflow. In addition, 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 or the blood-aqueous barrier. Latanoprost has no or negligible effects on the intraocular blood circulation when used at the human clinical dose, as studied in monkeys. However, mild to moderate conjunctival or episcleral hyperaemia may occur during topical treatment.

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. Latanoprost in clinical doses has not been found to have any significant pharmacologic effects on the cardiovascular or respiratory systems.

Timolol

Timolol maleate is a β_1 and β_2 (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by decreasing the formation of aqueous humour in the ciliary epithelium. The precise mechanism of action is not clearly established.

Xalacom

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.

Clinical Trials

Two 6-month, randomised, double-blind, multicentre clinical studies were conducted to compare the IOP-lowering effect of Xalacom dosed once daily to latanoprost 0.005% dosed once daily and timolol 0.5% dosed twice daily.

The inclusion criteria for patients in both studies consisted of adults with diagnoses of primary open angle glaucoma, pigmentary glaucoma, capsular glaucoma or ocular hypertension. Patients previously on IOP reducing therapy required an IOP at enrolment of ≥ 25 mmHg. Patients not previously on IOP reducing therapy required an IOP of ≥ 30 mmHg on enrolment. In the two studies, 92% and 84% of patients were reported to have been on IOP reducing therapy within 3 months prior to study start. Approximately 70% of these patients were on timolol therapy.

The mean diurnal IOP-lowering effect of Xalacom was greater (1 to 3 mmHg) than that produced by monotherapy with either latanoprost 0.005% or timolol 0.5%. However, there are no data to show the optimal dose of these agents in combination.

Open label extensions of the 2 studies mentioned above were conducted for up to an additional 6 months. The IOP lowering effect of Xalacom was maintained during this period.

5.2 Pharmacokinetic properties

Latanoprost

Absorption

Latanoprost is an isopropyl ester pro drug which is inactive, but after hydrolysis by esterases in the cornea to the acid of latanoprost, becomes biologically active.

The pro drug is well absorbed through the cornea and all the drug that enters the aqueous humour is hydrolysed during the passage through the cornea.

Distribution

Studies in man indicate that the peak concentration in the aqueous humour, approximately 30 ng/mL, is reached about two hours after topical administration of latanoprost alone. After topical application in monkeys latanoprost is distributed primarily in the anterior segment, the conjunctivae and the eye lids. Only minute quantities of the drug reach the posterior segment.

Reduction of the intraocular pressure in man starts about three to four hours after administration of latanoprost alone and maximum effect is reached after 8 to 12 hours. Pressure reduction is maintained for at least 24 hours.

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%.

Metabolism and Excretion

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 µg/day). The half life of timolol in plasma is about 6 hours. Timolol is extensively metabolised in the liver. The metabolites are excreted in urine together with some unchanged timolol.

Xalacom

No pharmacokinetic interactions between latanoprost and timolol have been observed although the aqueous humour concentrations of the acid of latanoprost tended to be higher 1 to 4 hours after administration of the combination product compared to monotherapy with either agent.

5.3 Preclinical safety data

Genotoxicity

Mutagenicity studies with Xalacom have not been conducted.

Latanoprost was not mutagenic in gene mutation assays in bacteria and mouse lymphoma L5178Y cells and was negative in studies of unscheduled DNA synthesis. Chromosome aberrations were observed with human lymphocytes *in vitro* but latanoprost did not induce micronucleus formation *in vivo*.

In vitro and *in vivo* studies with timolol maleate did not reveal a mutagenic potential.

Carcinogenicity

Carcinogenicity studies with Xalacom have not been conducted.

Latanoprost was not carcinogenic in either rats or mice when administered by oral gavage at doses up to 170 µg/kg/day for 24 and 20 months respectively.

No evidence of carcinogenicity was observed with timolol maleate at oral doses up to 100 mg/kg/day in rats and 50 mg/kg/day in mice. However, there was a statistically significant

increase in the incidence of adrenal phaeochromocytomas in male rats administered 300 mg/kg/day. In female mice, statistically significant increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary carcinomas were found at 500 mg/kg/day. The increased incidence of mammary tumours was considered to be attributed to a species specific elevation in serum prolactin.

Animal Toxicity

No adverse ocular or systemic effects were seen in rabbits treated topically with fixed combinations of latanoprost and timolol maleate for up to 52 weeks or with concomitantly administered latanoprost and timolol ophthalmic solutions for 4 weeks.

In long-term ocular toxicity studies in monkeys, latanoprost has been shown to induce increased iris pigmentation. The pigmentation did not progress upon discontinuation of treatment. The results from pre-clinical studies have demonstrated that the primary mechanism of increased pigmentation is stimulation of melanin production in melanocytes of the iris stroma. There is no evidence of melanocyte proliferation.

Long-term ocular administration of latanoprost at a dose of 6 µg/eye/day (4 times the daily human dose) to cynomolgus monkeys has also been shown to induce an increase or widening in the palpebral fissure. This effect was reversible upon discontinuation of the drug.

Timolol maleate did not produce any adverse ocular effects in rabbits and dogs, when administered as multiple daily topical doses for up to 52 and 104 weeks, respectively.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Monobasic sodium phosphate monohydrate,
Dibasic sodium phosphate,
Hydrochloric acid,
Sodium hydroxide,
Water for injections,
Benzalkonium chloride (0.20 mg/mL) (as a preservative agent).

6.2 Incompatibilities

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with benzalkonium chloride, the preservative used in Xalacom. If such drugs are used they should be administered with an interval of at least five (5) minutes between applications. Similarly several contact lens soaking solutions contain thiomersal.

Xalacom contains benzalkonium chloride which may be absorbed by contact lenses. Several contact lens soaking solutions contain thiomersal which may also form a precipitate with the benzalkonium chloride. Therefore contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store unopened bottle at 2°C to 8°C. Refrigerate. Do not freeze.

Store opened bottle below 25°C. Store in the outer cardboard carton. To be used within 4 weeks after opening.

Protect from light.

6.5 Nature and contents of container

Xalacom is supplied in packs of 1 x 2.5 mL and 3 x 2.5 mL*** filled in a polyethylene container.

*** Pack size not available.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Latanoprost

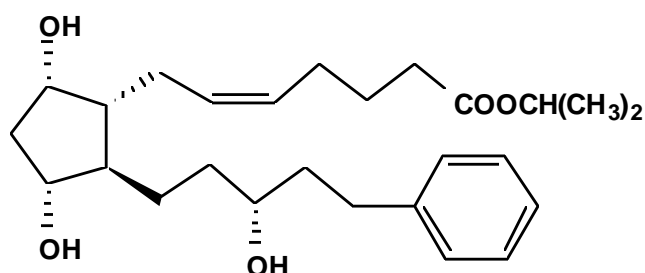
It has a molecular weight of 432.58. It is a colourless to slightly yellow oil which is practically insoluble in water, freely soluble in ethanol, ethyl acetate, isopropanol, methanol, acetone and octanol, and very soluble in acetonitrile.

Sixty four isomers of latanoprost are possible however, for Xalacom it is purified as a single isomer.

Chemical structure

The chemical name of latanoprost is isopropyl-(Z)-7[(1R,2R,3R,5S) 3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenyl-1-pentyl]cyclopentyl]-5-heptenoate, according to IUPAC. Its molecular formula is C₂₆H₄₀O₅.

The chemical structure is as follows:



CAS number

130209-82-4.

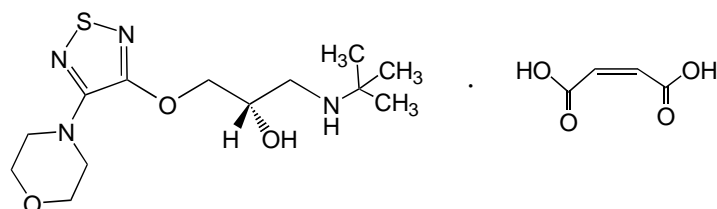
Timolol maleate

Timolol maleate is a beta-adrenergic receptor blocking agent. It has a molecular weight of 432.50. It is a white to off-white crystalline powder which is soluble in water, alcohol and practically insoluble in ether.

Chemical structure

The chemical name of timolol maleate is (S)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt). Its molecular formula is $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$.

The chemical structure is as follows:



CAS number

26921-17-5.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
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9. DATE OF FIRST APPROVAL

02 January 2002

10. DATE OF REVISION

21 February 2020

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatting according to new Australian PI template
1, 3, 5, 6	Editorial
8	Sponsor address change