PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# PrXALACOM®

Latanoprost and timolol ophthalmic solution

Solution, latanoprost 50 mcg/mL and timolol 5 mg/mL as timolol maleate, Ophthalmic

Prostaglandin $F_{2\alpha}$ Analogue and Beta-adrenergic Receptor Blocker

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## RECENT MAJOR LABEL CHANGES

None at the time of most recent authorization

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**Sections or subsections that are not applicable at the time of authorization are not listed.**


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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

XALACOM (latanoprost and timolol maleate) is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-adrenergic blocking agents, prostaglandins, or other IOP lowering agents AND when the use of XALACOM (the combination drug) is considered appropriate.

#### 1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

#### 1.2 Geriatrics

Geriatrics: Based on the data submitted and reviewed by Health Canada, there is no overall difference in the safety and efficacy of XALACOM use in the geriatric patient population.

### 2 CONTRAINDICATIONS

Latanoprost and timolol maleate 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 not controlled with pace-maker, overt cardiac failure, or cardiogenic shock.
- known hypersensitivity to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

- The use of XALACOM may be considered in patients who require both timolol and latanoprost. It has not been fully investigated whether patients who are adequately controlled with timolol twice daily plus latanoprost once daily will be effectively controlled with XALACOM once daily. The IOP lowering effect of XALACOM once daily may be less than that seen with the concomitant administration of timolol twice daily and latanoprost once daily based on the results from a short term clinical trial. For details of information obtained from the clinical trial, please refer to the 14 CLINICAL TRIALS section.
- XALACOM contains benzalkonium chloride which may be absorbed by contact lenses. Several contact lens soaking solutions contain thimerosal which may also form a

precipitate with benzalkonium chloride (see 9.4 Drug-Drug Interactions) Therefore, contact lenses should be removed before installation of the eye drops and may be reinserted after 15 minutes.

- XALACOM should not be used to initiate therapy

### 4.2 Recommended Dose and Dosage Adjustment

The recommended adult (including the elderly) dosage of XALACOM is one drop in the affected eye(s) once daily.

Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

### 4.4 Administration

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

### 4.5 Missed Dose

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

## 5 OVERDOSAGE

There is no human data available on overdosage with XALACOM.

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

Apart from ocular irritation and conjunctival or episcleral hyperemia, the ocular effects of latanoprost administered at high doses are not known. Intravenous infusion of up to 3 mcg/kg in healthy volunteers induced no symptoms, but a dose of 5.5-10 mcg/kg caused nausea, abdominal pain, dizziness, fatigue, hot flashes, and sweating. These events were mild to moderate in severity and resolved without treatment within 4 hours after terminating the infusion.

If overdose with XALACOM occurs, treatment should be symptomatic.

If XALACOM is accidentally ingested the following information may be useful: One bottle contains 125 mcg latanoprost and 12.5 mg timolol. Both timolol and latanoprost are extensively metabolized in the liver. In fact, more than 90% of latanoprost is metabolized during the first pass through the liver.

| |
|---|
| For management of a suspected drug overdose, contact your regional poison control centre. |

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 1 – Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Ophthalmic | Solution / fixed combination of latanoprost 50 mcg / mL and timolol 5 mg / mL as timolol maleate | Benzalkonium chloride, disodium hydrogen phosphate anhydrous, hydrochloric acid, sodium chloride, sodium dihydrogen phosphate monohydrate, sodium hydroxide and water for injection |

XALACOM is a sterile, isotonic, buffered, clear and colorless aqueous solution. One drop contains approximately 1.5 mcg of latanoprost and 150 mcg of timolol. XALACOM is intended for topical administration on the eye.

XALACOM is supplied in a 5 mL plastic ophthalmic dispenser bottle with a dropper tip, screw cap and tamper proof polyethylene overcap.

Each bottle contains 2.5 mL of XALACOM corresponding to approximately 80 drops of solution.

XALACOM is supplied as a sterile, isotonic, buffered, clear and colorless aqueous solution with a pH of approximately 6.0 and an osmolality of approximately 290 mOsmol/kg. Each mL contains 50 micrograms (mcg) of latanoprost and 5 mg of timolol (6.83 mg timolol maleate).

Non-medicinal ingredients: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water for injection. Benzalkonium chloride 0.02% is added as a preservative. If required, the pH of the solution is adjusted with hydrochloric acid and/or sodium hydroxide.

## 7 WARNINGS AND PRECAUTIONS

### General

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of ocular epithelial surface (see PATIENT MEDICATION INFORMATION).

There is no or limited experience with latanoprost in inflammatory, neovascular, chronic angle closure or congenital glaucoma**,** open angle glaucoma in pseudophakic patients and pigmentary glaucoma.

**Concomitant therapy:** XALACOM may interact with other drugs (see 9.4 Drug-Drug Interactions**)**. The effect on intraocular pressure or the known effects of systemic beta-adrenergic blocking agents may be exaggerated when XALACOM is given to patients already receiving an oral beta-blocking agent. The use of two local 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.

**Systemic Effects:** Like other topically applied ophthalmic agents, is absorbed systemically. Due to the beta-adrenergic component timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur including aggravation of Prinzmetal's angina, aggravation of peripheral and central circulatory disorders, bradycardia, and hypotension.

Incidence of systemic adverse drug reactions after topical ophthalmic administration is lower than for systemic administration. The systemic absorption can be reduced by using nasolacrimal occlusion or closing the eyelids for 2 minutes (see 4.4 Administration).

**Cardiovascular**

**Cardiac reactions:** Death associated with cardiac failure has been reported. Cardiac failure should be adequately controlled before beginning treatment. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked. At the first sign of cardiac failure, XALACOM should be discontinued. Due to its negative effect on conduction time, beta-adrenergic blocking agents should only be given with caution to patients with first degree heart block.

**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.

**Driving and Operating Machinery**

In common with other eye preparations, installation of eye drops may cause transient blurring of vision.

**Endocrine and Metabolism**

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subjected to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Therapy with beta-adrenergic blocking agents may mask certain symptoms of hyperthyroidism. Abrupt withdrawal of beta-adrenergic blocking agent therapy may precipitate a worsening of symptoms.

**Hepatic/Biliary/Pancreatic**

XALACOM has not been studied in patients with hepatic impairment and therefore should be used with caution in such patients.

**Neurologic**

**Muscle Weakness:** Beta-adrenergic blocking agents have been reported to rarely increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms (e.g. diplopia, ptosis, generalized weakness).

**Ophthalmologic**

Latanoprost has been reported to cause darkening, thickening and lengthening of eye lashes (see 8.5 Post-Market Adverse Reactions).

Based on spontaneous reports, very rare cases of darkening of the palpebral skin have been reported with the administration of latanoprost ophthalmic solution (see 8.5 Post-Market Adverse Reactions).

Due to the prostaglandin component latanoprost, XALACOM should be used with caution in patients with a history of herpetic keratitis. XALACOM 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.

This product contains benzalkonium chloride as a preservative, which may be absorbed by soft contact lenses. Remove contact lenses before administration of XALACOM. Contact lenses may be reinstalled 15 minutes after administering XALACOM.

Ophthalmic beta-adrenergic blocking agents may induce dryness of eyes. These agents should be used prescribed with caution in patients with corneal diseases.

Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost ophthalmic solution. 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 edema. XALACOM should be used with caution in these patients.

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

**Changes to Pigmented Tissues**: Latanoprost, the prostaglandin component contained in XALACOM, may gradually change the eye color, by increasing the amount of brown pigment in the iris. The color change is due to increased melanin content in stromal melanocytes on the iris rather than to an increase in the number of melanocytes. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. The change in iris colour occurs slowly and may not be noticeable for several months to years. The long term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye is currently unknown. Patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased iris pigmentation ensues.

This effect has predominantly been seen in patients with mixed colored irides (i.e. blue/gray-brown, green-brown, or yellow-brown). In patients with homogeneously blue, gray, green or brown eyes, the change has only rarely been seen during two years of treatment in clinical trials. The change in iris color occurs slowly, and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change. Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation in the treated eye and thus, permanent heterochromia between the eyes. The increased pigmentation is permanent.

There is no evidence of melanin from iris melanocytes in trabecular meshwork in clinical studies which supports the lack of hyperpigmentation of the trabecular meshwork as a result of latanoprost treatment. In addition, no difference in iridial pigment epithelial melanin content has been observed between the latanoprost-treated eyes with increased iris pigmentation and untreated eyes from quantitative morphologic investigation of iridial specimens following colour change. Histopathologically, the increase in pigmentation was limited to a minor increase in the size of the melanin granules in the iris stroma.

**Closed Angle Glaucoma:** XALACOM should not be used alone in the treatment of acute closed angle glaucoma. In patients with closed angle glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Latanoprost and Timolol Maleate have little or no effect on the pupil.

**Peri-Operative Considerations**

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 anesthesia in surgical procedures. Protracted severe hypotension during anesthesia 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.

**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.

**Renal**

XALACOM has not been studied in patients with renal impairment and therefore should be used with caution in such patients.

**Reproductive Health: Female and Male Potential**

- **Fertility**

Latanoprost has not been found to have any effect on male or female fertility in animal studies. Reproduction and fertility studies of timolol maleate in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

**Respiratory**

**Respiratory Reactions:** Severe respiratory reactions including death due to bronchospasm in patients with asthma and rarely death associated with cardiac failure have been reported following administration of beta-adrenergic blocking agents.

**Respiratory Disorders:** Due to the beta-adrenergic component timolol maleate, 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.

**Sensitivity/Resistance**

**Anaphylactic Reactions:** While taking beta-adrenergic blocking agents, patients with a history of atopy or severe anaphylactic reaction to a variety of allergens may be more sensitive to repeated challenge. These could include environmental, diagnostic or therapeutic allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

### 7.1 Special Populations

#### 7.1.1 Pregnant Women

No reproduction toxicity studies have been conducted with XALACOM. 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 characterized by increased incidences of late resorption and reduced fetal weight at 5 mcg/kg/day IV and total litter resorption at ≥ 50 mcg/kg/day IV. No embryofetal effects were seen in rabbits at 1 mcg/kg/day IV and in rats at up to 250 mcg/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 mcg/kg/day. At higher doses, increases in resorptions and fetal variations (14 ribs and hypoplastic sternebrae) were noticed in mice (1000 mcg/kg/day) and increased resorption in rabbits (≥ 90 mcg/kg/day). In rats, delayed ossification was seen ≥ 50 mcg/kg/day and a decreased number of caudal vertebral bodies and arches and an increase in hypoplastic sternebrae were noted at 500 mcg/kg/day.

For additional information, see 16 NON-CLINICAL TOXICOLOGY.

XALACOM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### 7.1.2 Breast-feeding

There are limited experimental animal and no human data available on the pharmacokinetics of latanoprost 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, XALACOM should be used with caution in nursing women.

#### 7.1.3 Pediatrics

**Pediatrics (< 18 years of age):** The safety and efficacy of the use of XALACOM in children has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

The most commonly reported ocular adverse reactions in controlled clinical trials, that may be associated with combination therapy of latanoprost and timolol maleate were eye irritation (12.4 %), eye hyperaemia (7.4 %), abnormal vision (6.6 %), conjunctivitis (3.0 %) and corneal disorder (3.0 %) (see 8.2 Clinical Trial Adverse Reactions). The most commonly reported systemic adverse reactions in controlled clinical trials, that may be associated with combination therapy of latanoprost and timolol maleate were upper respiratory track infection (6.1 %), hypertension (3.8 %), influenza-like symptoms (2.5 %) and headache (2.3 %) (see 8.2 Clinical Trial Adverse Reactions).

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

XALACOM was generally well tolerated. No adverse events specific to XALACOM have been observed in clinical studies. The adverse events have been limited to those that were reported previously with latanoprost and/or timolol maleate.

XALACOM was evaluated for safety in 394 patients with open-angle glaucoma or ocular hypertension in three long-term studies. Two percent (2%) of patients discontinued therapy with XALACOM due to adverse events.

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

**Table 2. Ocular adverse events (AE) that occurred in ≥ 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 |
| **Vision** | | | |
| 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 (burning, grittiness, itching, stinging and foreign body sensation) | 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) |
| **Skin & Appendages** | | | |
| 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) | - |
| **Central & Peripheral Nervous System** | | | |
| Optic atrophy | 2 (0.5) | 3 (0.7) | 6 (1.4) |
| 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 3. 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** | | | |
| 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** | | | |
| 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) |
| **Cardiovascular** | | | |
| Hypertension | 15 (3.8) | 6 (1.4) | 10 (2.4) |
| Hypertension aggravated | 2 (0.5)* | 1 (0.2)* | 1 (0.2)* |
| **Metabolic & Nutrition** | | | |
| 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) |
| **Central & Peripheral Nervous System** | | | |
| Dizziness | 2 (0.5) | 4 (1.0) | 1 (0.2) |
| Headache | 9 (2.3) | 15 (3.6) | 5 (1.2) |
| **Musculo-Skeletal** | | | |
| Arthritis | 8 (2.0) | 5 (1.2) | 4 (1.0) |

| | | | |
|---|---|---|---|
| **Psychiatric** | | | |
| 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 & Appendages** | | | |
| Bullous eruption | - | 1 (0.2) | - |
| Rash | 5 (1.3) | 3 (0.7) | 2 (0.5) |
| **Resistance Mechanisms** | | | |
| Infection | 4 (1.0) | 6 (1.4) | 6 (1.4) |
| **Gastro-Intestinal** | | | |
| Dyspepsia | 2 (0.5) | 4 (1.0) | 1 (0.2) |
| **Urinary** | | | |
| Cystitis | 1 (0.3) | 5 (1.2) | - |
| 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

Based on evidence from consecutive photographs, increased iris pigmentation was observed in 16-20% of patients treated with XALACOM for up to one year. The most frequent findings of increased iris pigmentation were in the known high-risk eye color groups, i.e. those with green-brown, yellow-brown, and blue/gray-brown irises. In patients with homogeneously blue, grey, green or brown eyes, the change was rarely observed. Darkening, thickening and lengthening of eye lashes were observed in 37.4% of patients.

### 8.5 Post-Market Adverse Reactions

The following additional adverse events that have been reported with latanoprost and timolol eye drops:

**Latanoprost**

| System Organ Class | Adverse Drug Reactions |
|---|---|
| Cardiac disorders | Angina unstable, angina, palpitations |

| System Organ Class | Adverse Drug Reactions |
|---|---|
| Eye disorders | Macular oedema, corneal erosion, punctate keratitis, corneal oedema, pseudopemphigoid of ocular conjunctiva, trichiasis, vision blurred, eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes), localised skin reaction on the eyelids, iris cyst, periorbital and lid changes resulting in deepening of the eyelid sulcus, darkening of the palpebral skin of the eyelids |
| Infections and infestations | Herpetic keratitis |
| Gastrointestinal disorders | Vomiting, nausea |
| Respiratory, thoracic and mediastinal disorders | Acute asthma attacks, asthma aggravation, asthma, |
| Skin and subcutaneous tissue disorders | Pruritus |

**Timolol Maleate (topical formulation)**

| System Organ Class | Adverse Drug Reactions |
|---|---|
| Cardiac disorders | Cardiac arrest, cardiac failure, heart block, atrioventricular block, congestive heart failure, worsening of angina pectoris, arrhythmia, bradycardia, palpitation |
| Ear and labyrinth disorders | Tinnitus |
| Eye disorders | Choroidal detachment (following filtration surgery), corneal erosion, diplopia, decreased corneal sensitivity, signs and symptoms of ocular irritation (e.g., tearing, redness), dry eyes, ptosis, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), vision blurred |
| Gastrointestinal disorders | Retroperitoneal fibrosis, abdominal pain, vomiting, diarrhoea, dry mouth, dysgeusia, nausea |
| General disorders and administration site conditions | Oedema, asthenia, fatigue |
| Immune system disorders | Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, pruritus, localized and generalized rash |
| Metabolism and nutrition disorders | Masked symptoms of hypoglycaemia in diabetic patients, anorexia |
| Musculoskeletal and connective tissue disorders | Myalgia, systemic lupus erythematosus |

| System Organ Class | Adverse Drug Reactions |
|---|---|
| Nervous system disorders | Cerebral vascular accident, cerebral ischemia, increase in signs and symptoms of myasthenia gravis, paraesthesia, somnolence, syncope |
| Psychiatric disorders | Behavioural changes and psychic disturbances including, confusion, hallucinations, anxiety, disorientation, nervousness, nightmares, memory loss |
| Reproductive system and breast disorders | Sexual dysfunction, decreased libido, impotence, Peyronie's disease |
| Respiratory, thoracic and mediastinal disorders | Respiratory failure, pulmonary oedema, bronchospasm (predominantly in patients with pre-existing bronchospastic disease), nasal congestion |
| Skin and subcutaneous tissue disorders | Psoriasiform rash, pseudopemphigoid, exacerbation of psoriasis, alopecia |
| Vascular disorders | Claudication, cold hands and feet, hypotension, Raynaud's phenomenon |

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.

## 9 DRUG INTERACTIONS

### 9.2 Drug Interaction Overview

No specific interaction studies have been performed with XALACOM.

Patients who are receiving treatment with XALACOM and an oral beta-adrenergic blocking agent should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two 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 timolol ophthalmic drops are administered with oral calcium channel blockers, catecholamine-depleting drugs or beta-adrenergic blocking agents, antiarrythmics (including amiodarone and quinidine), digitalis glycosides, parasympathomimetics, narcotics, guanethidine and monoamine oxidase (MAO) inhibitors.

Potentiated systemic beta adrenergic 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 epinephrine.

Beta-adrenergic blocking agents may increase the hypoglycemic effect of antidiabetic agents.

In vitro studies have shown that precipitation occurs when eye drops containing thimerosal 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 5 minutes between applications. Similarly, several contact lens soaking solutions contain thimerosal (see 4.4 Administration).

### 9.4 Drug-Drug Interactions

**Table 4 - Established or Potential Drug-Drug Interactions**

| [Proper/Common name] | Source of Evidence | Effect | Clinical comment |
|---|---|---|---|
| Beta-adrenergic blocking agent | T | Additive effect of beta-blockade, both systemic and on intraocular pressure. | Concomitant use of two topical beta-adrenergic blocking agents is not recommended. |
| Calcium channel blockers, catecholamine-depleting drugs or beta-adrenergic blocking agents, antiarrythmics (including amiodarone and quinidine), digitalis glycosides, parasympathomimetics, narcotics, guanethidine, monoamine oxidase (MAO) inhibitors | T | Potential additive effects resulting in hypotension and /or marked bradycardia. | |
| CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) | C | Potentiated systemic beta-adrenergic blockade (e.g., decreased heart rate, depression). | |
| Prostaglandin / prostaglandin analog / prostaglandin derivative | C | Elevations in Intraocular pressure following concomitant ophthalmic administration. | Use of two or more prostaglandins, prostaglandin analogs, or prostaglandin derivatives is not recommended. |

| | | | |
|---|---|---|---|
| Thimerosal | T | Precipitation occurs when mixed. | Thimerosal usage with latanoprost should be administered with an interval of at least 5 minutes between applications. |

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

XALACOM consists of two components: latanoprost and timolol maleate. Each mL of XALACOM contains latanoprost 50 micrograms and timolol maleate 6.8 mg equivalent to 5 mg timolol. These two components decrease elevated intraocular pressure (IOP) by different mechanisms of action.

**Latanoprost** is a prostanoid selective FP receptor agonist which reduces the IOP by increasing the outflow of aqueous humor. 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. **Timolol maleate** is a $beta_1$ and $beta_2$ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. Timolol lowers the IOP by decreasing the formation of aqueous humor in the ciliary epithelium. The precise mechanism of action is not clearly established. The combined effect of these two agents administered as XALACOM once daily results in additional intraocular pressure reduction compared to either component administered alone separately. For details of information obtained from Clinical Trials with XALACOM, please refer to 14 CLINICAL TRIALS section.

### 10.3 Pharmacokinetics

**Table 5 - Summary of latanoprost Pharmacokinetic Parameters in aqueous humor in adults**

| | $C_{max}$ | $T_{max}$ | $t_{½}$ (h) | $AUC_{0-\infty}$ | CL | Vd |
|---|---|---|---|---|---|---|
| **Single dose mean** | 30 ng / mL | 2 hours | 2.3 | 206 ng·hr / mL | N/A | N/A |

**Table 6 - Summary of latanoprost Pharmacokinetic Parameters in plasma in adults**

| | $C_{max}$ | $T_{max}$ | $t_{½}$ (h) | $AUC_{0-\infty}$ | CL | Vd |
|---|---|---|---|---|---|---|
| **Single dose mean** | 29 pg / mL | 5 minutes | 0.3 | 448 pg·min / mL | 7 mL / min / kg | 0.16 ± 0.02 L / kg |

**Table 7 - Summary of timolol Pharmacokinetic Parameters in aqueous humor in adults**

| | $C_{max}$ | $T_{max}$ | $t_{½}$ (h) | $AUC_{0-\infty}$ | CL | Vd |
|---|---|---|---|---|---|---|
| **Single dose mean** | 1167 ng / mL | 1 hour | 3.9 | 3644 ng·hr / mL | N/A | N/A |

**Table 8 - Summary of timolol Pharmacokinetic Parameters in plasma in adults**

| | $C_{max}$ | $T_{max}$ | $t_{½}$ (h) | $AUC_{0-\infty}$ | CL | Vd |
|---|---|---|---|---|---|---|
| **Single dose mean** | ~ 1 ng / mL | 10 – 20 minutes | ~ 6 hours | 5 ng·hr / mL | N/A | N/A |

**Latanoprost**

**Absorption:** Latanoprost is an isopropyl ester prodrug which is inactive but becomes biologically active after hydrolysis to the acid of latanoprost. The prodrug is well absorbed through the cornea and all drug that enters the aqueous humor is hydrolysed by esterases during the passage through the cornea. Studies indicate that the maximum concentration in the aqueous humor, approximately 30 ng/mL, is reached about 2 hours after topical administration of latanoprost alone. 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%.

**Distribution:** The acid of latanoprost has a small volume of distribution of 0.16 L/kg.

**Metabolism:** Latanoprost is an isopropyl ester prodrug which is inactive but becomes biologically active after hydrolysis to the acid of latanoprost. The main metabolism occurs in the liver. There is practically no metabolism of the acid of latanoprost in the eye. The main metabolites, 1,2-dinor and 1,2,3,4- tetranor metabolites, exert no or weak biological activity

**Elimination:** The acid of latanoprost has a plasma clearance of 0.40 L/h/kg and a rapid half-life in plasma of 17 minutes. The main metabolites, 1,2-dinor and 1,2,3,4- tetranor metabolites, exert no or weak biological activity in animal studies and are excreted primarily in the urine.

**Timolol**

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

**Metabolism:** Timolol is extensively metabolized in the liver.

**Elimination:** The half-life of timolol in plasma is about 6 hours. The metabolites, and unchanged timolol, are excreted in the urine.

**XALACOM**

No pharmacokinetic interactions between latanoprost and timolol have been observed although the aqueous humor 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 latanoprost or timolol.

**Special Populations and Conditions**

**Pediatrics:** Differences in the pharmacokinetics of XALACOM in this population has not been investigated.

**Geriatrics:** Differences in the pharmacokinetics of XALACOM in this population has not been investigated.

**Sex:** Differences in the pharmacokinetics of XALACOM in this population has not been investigated.

**Ethnic Origin:** Differences in the pharmacokinetics of XALACOM in this population has not been investigated.

**Hepatic Insufficiency:** No studies have been performed to investigate the influence of demographic characteristics on the pharmacokinetics of XALACOM due to the inherent difficulties in measuring the drug concentrations after topical administration on the eyes.

**Renal Insufficiency:** No studies have been performed to investigate the influence of demographic characteristics on the pharmacokinetics of XALACOM due to the inherent difficulties in measuring the drug concentrations after topical administration on the eyes.

## 11 STORAGE, STABILITY AND DISPOSAL

Store unopened bottle under refrigeration (2°C to 8°C). Protect from light. Once opened, the 5 mL container may be stored at room temperature up to 25ºC for 10 weeks. Protect from light.

## 12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this drug product.

**PART II: SCIENTIFIC INFORMATION**

## 13 PHARMACEUTICAL INFORMATION

### Drug Substance

XALACOM contains latanoprost and timolol maleate.

**Latanoprost:**

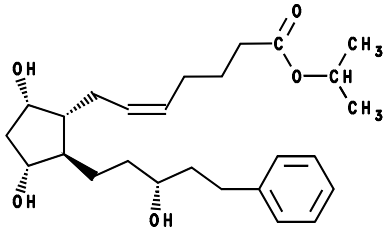
Proper Name: latanoprost

Chemical Names: 1) Isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate

2) 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_2$ α-isopropyl ester

Molecular formula and molecular Mass: $C_{26}H_{40}O_5$ and 432.58

Structural Formula:



Physicochemical Properties:

| | |
|---|---|
| Physical Form | Colourless to slightly yellow oil. |
| Solubility | Very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol and octanol, and practically insoluble in water. |

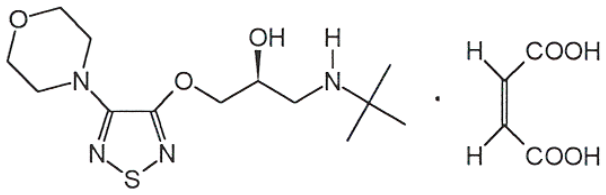
**Timolol Maleate:**

Proper Name: timolol maleate

Chemical Name: S)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt)

Molecular formula and molecular mass: $C_{13}H_{24}N_4O_3S \bullet C_4H_4O_4$ and 432.50

Structural Formula:



Physicochemical Properties:

| | |
|---|---|
| Physical form | White to off-white crystalline powder |
| Solubility | Soluble in water, alcohol and practically insoluble in ether. |
| pH | 3.8 - 4.3 (2% in Water) |
| pKa | 9.2 |
| Melting Point | 200 - 202ºC with decomposition |

## 14 CLINICAL TRIALS

### 14.1 Clinical Trials by Indication

**Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-adrenergic blocking agents, prostaglandins, or other IOP lowering agents**

Two 6-month, randomized, double-masked, multicenter clinical studies were conducted to compare the IOP-lowering effect of XALACOM (latanoprost and timolol maleate) dosed once daily to latanoprost 50 mcg/mL dosed once daily and timolol 5 mg/mL dosed twice daily.

The inclusion criteria in both studies consisted of adults with a diagnosis of primary open angle glaucoma (72%), ocular hypertension (20%), pigmentary glaucoma (2%), exfoliative glaucoma (4%) and other (2%). Patients enrolled could have been on previous therapy (88%) or not on medication (12%) and were required to have an IOP of ≥ 25 mmHg if on medication or ≥30 mmHg if not on therapy at enrollment. There was no restriction on the number or type of glaucoma medications taken prior to study entry. The distribution of patients at enrollment on glaucoma medication and not on glaucoma medication were similar in each of the three treatment groups. Approximately 70% of patients were on timolol therapy prior to enrollment. In the studies the baseline study visit was preceded by a 2-4 weeks run-in period on timolol 5 mg/mL bid.

Table 10 and 11 shows the mean diurnal IOP reductions at the end of the treatment XALACOM (FC) and the individual monotherapies for all patients. All values are statistically significant.

**Table 9. Summary of patient demographics for clinical trials in the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-adrenergic blocking agents, prostaglandins, or other IOP lowering agents**

| Study # | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| 004 | Multi-center, randomized, double masked active controlled | Fixed dose (XALACOM (FC) once daily, latanoprost one daily, timolol twice daily), ophthalmic, 6 months | FC: 140<br>Latanoprost: 147<br>Timolol: 149<br>Total: 436 | 64<br>(18 – 90) | 196M<br>240F |
| 005 | Multi-center, randomized, double masked active controlled | Fixed dose (XALACOM once daily, latanoprost one daily, timolol twice daily), ophthalmic, 6 months | FC: 138<br>Latanoprost: 140<br>Timolol: 140<br>Total: 418 | 62<br>(24 – 87) | 215M<br>203F |

**Table 10 - Results of study 004 in the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-adrenergic blocking agents, prostaglandins, or other IOP lowering agents**

| Primary Endpoint | Mean Diurnal IOP reduction between treatments |
|---|---|
| Mean diurnal IOP reduction between treatments | FC vs latanoprost: -1.2 mmHg p<0.001<br>FC vs timolol: -1.9 mmHg p<0.001 |

**Table 11 - Results of study 005 in the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-adrenergic blocking agents, prostaglandins, or other IOP lowering agents**

| Primary Endpoint | Mean Diurnal IOP reduction between treatments |
|---|---|
| Mean diurnal IOP reduction between treatments | FC vs latanoprost: -1.0 mmHg p=0.02<br>FC vs timolol: -2.9 mmHg p<0.001 |

Patients enrolled could have been on previous therapy (88%) or not on medication (12%). Analysis on the primary efficacy endpoints for studies 004 and 005 indicate that inclusion or exclusion of patients who are not on medication prior to enrollment (12%) had no influence on statistical outcome of efficacy observed in the studies.

In clinical practice, the appropriate value of a target IOP (an IOP level that would be considered a clinical success) is determined by the physician for each patient. Information from the recent Advanced Glaucoma Intervention Study (AGIS) indicates that an IOP of 18 mmHg or less is correlated with reduced progression of visual field defects associated with glaucoma. A responder analysis was performed for the two studies and supports the value of XALACOM over the individual monotherapies as shown in Table 12.

**Table 12. Responder* rate within each treatment group for each designated threshold value.**

| Threshold value | Treatment Groups (%) | | |
|---|---|---|---|
| | FC<br>n = 278 | Latanoprost<br>n = 287 | Timolol<br>n = 289 |
| ≤ 18 | 12.9 | 4.9 | 3.8 |
| ≤ 19 | 20.5 | 12.5 | 6.9 |
| ≤ 20 | 30.2 | 20.2 | 11.8 |
| ≤ 21 | 42.4 | 27.9 | 18.0 |

*Responder for the analysis was defined as that all IOP measurements for a patient were equal to or below the stated threshold value. All values are statistically significant.

A short term double blind, controlled, crossover study (n=190) was performed to evaluate XALACOM (FC) versus the individual monotherapies (latanoprost once daily and timolol 5 mg/mL twice daily administered separately, uFC) in maintaining the IOP of well-controlled patients on the combination of the individual monotherapies. In this study patients were randomized into one of two treatment sequences, (FC-UFC) or (UFC - FC) with each treatment in the sequence given for 6 weeks. The mean baseline IOP for the groups receiving FC-UFC and UFC -FC treatment sequences was, 17.2 mmHg and 17.1 mmHg respectively. Results from this short-term crossover study indicates that XALACOM maintained the IOP seen in the population at enrollment while the concomitant use of the individual monotherapies resulted in a decrease in the IOP. Overall, the mean IOP after FC treatment was 17.0 mmHg and was 15.9 mmHg following uFC treatment. The 95% CI for the difference in diurnal IOP between the two treatments after six weeks of dosing was 0.8 to 1.4 mmHg.

Open-label extensions of these studies were conducted for up to an additional 6 months. The IOP-lowering effect of XALACOM was maintained during this period.

There are no data to show the optimal dose of latanoprost and timolol in combination.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology

### Acute Toxicity

#### Latanoprost and timolol maleate

A single subcutaneous dose of 20 mL/kg, corresponding to 1 mg/kg of latanoprost and 100 mg/kg of timolol, was well tolerated in rats and the only finding was a local reaction at the site of injection (thickening of the skin).

#### Latanoprost

A single oral dose of 50 mg/kg and an intravenous dose of 2 mg/kg were well tolerated in mice and rats. In male dogs given an intravenous infusion of latanoprost, the minimum lethal dose was greater than 680 mcg/kg.

#### Timolol

The $LD_{50}$ values after oral administration was 1190 mg/kg in mice and 900 mg/kg in rats. The corresponding values after parenteral administration were 225 mg/kg (i.v.) and 383 mg/kg (i.p.), respectively. Infant rats were more sensitive than adult animals. In rabbits, the maximum nonlethal oral and intravenous doses were 485 mg/kg and 34 mg/kg, and the $LD_{50}$ values were 347 mg/kg and 16 mg/kg, respectively.

### Repeated Dose Toxicity

#### Latanoprost and timolol maleate

Local toxicity has been investigated after twice daily topical application in pigmented rabbits for 4 weeks. The daily dose of latanoprost was 3 mcg/eye and that of timolol was 300 mcg/eye. No local ocular irritation or changes at ophthalmological examinations were found and there were no macroscopic and microscopic alterations.

Chronic local and systemic toxicity has also been evaluated in pigmented rabbits. One drop once daily ocular administration, corresponding to 1.5 mcg/eye/day of latanoprost and 150 mcg/eye/day of timolol, produced no evidence of local irritation, and ocular or systemic toxicity, as assessed by ophthalmoscopy, tonometry, pachymetry, clinical chemistry, and complete gross and microscopic examinations. In conclusion, the application of latanoprost and timolol ophthalmic solution to the rabbit eye for 52 weeks was well tolerated.

#### Latanoprost

Ocular and systemic toxicity of latanoprost has been investigated in several animal species. Repeated intravenous doses of up to 340 mcg/kg/day for 4 weeks were well tolerated in rats, whereas intravenous doses of 100 mcg/kg/day and above induced hypersalivation and miosis during infusion followed by vomiting and sometimes liquid feces post-infusion in dogs.

Latanoprost was well tolerated and produced no evidence of ocular or systemic toxicity when administered to rabbits and cynomolgus monkeys at doses of up to 100 mcg/eye/day for 52 weeks and to rhesus monkeys at doses up to 20 mcg/eye for up to 104 weeks. However, in

cynomolgus and rhesus monkeys, latanoprost has been shown to induce increased pigmentation of the iris at doses from 2 mcg/day, with a dose-dependency in onset. An increase in palpebral fissure was also observed at doses from 6 mcg/eye/day in chronic ocular toxicity studies in monkeys. This could be due to a change in the supportive tissue around the eyelids. No changes could be detected histologically in the eyelids affected. This effect is reversible and occurs at doses well above the human clinical dose.

*Iris pigmentation*

The increased iridial pigmentation observed in monkeys and also in humans during chronic ocular treatment with latanoprost is considered to be a class effect of prostaglandins. It is of particular interest that naturally occurring prostaglandins such as $PGF_{2\alpha}$ and $PGE_2$ also cause increased pigmentation of the iris in cynomolgus monkeys. It should also be noted that both cynomolgus monkey and human iridial melanocytes express FP receptors in their cell membrane, and since latanoprost is a very selective FP receptor agonist, it implies that the effect is mediated by FP receptors in the melanocytes. It has been confirmed that there is no specific uptake of latanoprost in the melanin-containing tissues of the eye.

Studies on monkey and human melanocytes have shown that latanoprost has no proliferative effect on ocular melanocytes. In bilaterally sympathectomized rabbits, which were treated unilaterally with latanoprost and developed slightly increased iridial pigmentation in the treated eye, no difference in the number of melanocytes in iridial sections was found between the eyes exhibiting increased pigmentation and the control eyes. This confirms the results of *in vivo* and *in vitro* studies in primates showing a lack of proliferative effect of latanoprost on ocular melanocytes.

In a 104-week ocular toxicity study in rhesus monkeys, the iridial stroma exhibited a more intense pigmentation of the pigmented cells in all treated groups, but remained morphologically normal at the end of the treatment and recovery periods. A quantitative morphometric analysis showed an increase in the number of melanosomes in iridial melanocytes, and an increase in the cell area and ratio of granule area to cell area in the treated eyes when compared to the control eyes. However, in animals treated for 52 weeks following a recovery period of 104 weeks, no significant difference between treated and control eyes were observed at the end of the recovery period. These data suggest a minor modification in melanosome number and size with treatment and an apparent tendency towards reversibility after an extensive recovery period.

Morphological examination of three iridectomy specimens from patients indicated that the eye color change after long-term topical treatment with latanoprost is more likely produced by increased melanin density per melanocyte, or movement and rearrangement of cells in the tissue than by proliferation of melanocytes. Thus, there are no indications of any toxic effects of latanoprost on the pigment containing cells of the iris. In addition, results have shown that the increase of pigmentation is due to increased synthesis or turnover of melanin in the iridial melanocytes, and no proliferative changes occur during pigmentation.

**Timolol**

In rats, oral administration of timolol for 8 weeks was associated with increased spleen weights and splenic congestion at doses from 400 mg/kg/day, and decreases in body weight gain and mortality at 800 mg/kg/day. No changes were found at these dose levels after 7 weeks of treatment. In subchronic studies in dogs, oral doses from 100 mg/kg/day caused emesis and renal toxicity, and death occurred at 200 mg/kg/day. Timolol was well tolerated in dogs after repeated administration of oral doses up to 25 mg/kg/day for 54 weeks. The only treatment related findings were pharmacologic effects, including decreases in heart rates and slight increases in the PR and QT intervals, at doses from 5 mg/kg/day and above.

Timolol did not cause any adverse ocular effects in rabbits when administered as multiple daily topical doses up to 6 mg/eye/day for 52 weeks or in dogs after three times daily instillation at doses up to 1.5 mg/eye/day, five days a week, for 104 weeks.

**Carcinogenicity**

**Latanoprost**

No carcinogenic potential was indicated in rodents after oral doses of up to 200 mcg/kg/day. At this dose, the maximum plasma concentrations of acid of latanoprost in mice and rats were at least 50 and 13 times higher, respectively, than those in humans after a clinical dose of latanoprost in both eyes.

**Timolol**

No evidence of carcinogenicity was observed at oral doses up to 100 mg/kg/day in rats and 50 mg/kg/day in mice, which resulted in systemic exposures of approximately 7000-14000 times the exposure in humans after a maximum recommended ophthalmic dose of timolol. However, significant increases in adrenal pheochromocytomas were found in male rats administered 300 mg/kg/day. In female mice at 500 mg/kg/day, significant increases were observed in the incidence of benign and malignant pulmonary tumors, benign uterine polyps, and mammary adenocarcinomas. The increased incidence of mammary tumors was considered related to a species-specific elevation in serum prolactin.

**Reproductive and Developmental Toxicology**

**Latanoprost**

Latanoprost has no effects on fertility and general reproductive performance in male and female rats, and no teratogenic potential in rats or rabbits. No embryotoxicity was observed in rats after intravenous doses of up to 250 mcg/kg/day. However, latanoprost caused embryofetal toxicity, characterized by an increased incidence of late resorption and abortion, and by reduced fetal weight, in rabbits when administered intravenously at doses of 5 mcg/kg/day and above, whereas a dose of 1 mcg/kg/day had no effects. The effects on the fetal development are probably attributed to a marked luteolytic effect in rabbits, a class effect of prostaglandin $F_{2\alpha}$ and its analogues. However, this effect is minimal in humans.

**Timolol**

Reproduction and fertility studies in rats showed no adverse effects on male or female fertility at oral doses of 300 and 450 mg/kg/day, respectively. No teratogenic effects or embryofetal toxicity was observed in mice, rats or rabbits after oral doses up to 50 mg/kg/day (about 7000 times the systemic exposure in humans after a maximum therapeutic dose of timolol ophthalmic solution). Timolol did not cause any effects on peri- and postnatal development in mice and rats when administered orally at doses of up to 1000 and 500 mg/kg/day, respectively.

**Mutagenicity**

**Latanoprost**

Latanoprost was found negative in reverse mutation tests in bacteria, gene mutation test in mouse lymphoma and mouse micronucleus test. Chromosome aberrations were observed at cytotoxic concentrations *in vitro* with human lymphocytes. Similar effects have been reported with prostaglandin $F_{2\alpha}$, a naturally occurring prostaglandin, which indicates that this is a class effect. Additional mutagenicity studies on *in vitro/in vivo* unscheduled DNA synthesis in rats were negative and the conclusion is that latanoprost has no mutagenic potential.

**Timolol**

Timolol was not mutagenic *in vivo* in the mouse micronucleus test and cytogenetic assay, or *in vitro* in a neoplastic cell transformation assay. In the Ames test, statistically significant increases in revertants were found at the highest concentrations employed (5000 or 10000 mcg per plate) with tester strain TA 100, but not in the remaining three strains. However, the results of the *in vitro* microbial assay were not considered positive, because a ratio of the test to control revertants of 2 was never attained.

**Special Toxicology**

Local Tolerance: No local irritation or toxicity was observed after twice daily topical application of latanoprost and timolol ophthalmic solution on the rabbit eye for 4 weeks or once daily application for 52 weeks.

**PATIENT MEDICATION INFORMATION**

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PrXALACOM®**

**Latanoprost and timolol ophthalmic solution**

Read this carefully before you start taking **XALACOM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **XALACOM**.

**What is XALACOM used for?**

XALACOM is used to reduce eye pressure in patients with conditions called "open angle glaucoma" or "ocular hypertension". Both these conditions are related to an increase in pressure within the eye. If the high pressure is not reduced, it could damage your eyesight.

**How does XALACOM work?**

XALACOM contains two drugs, latanoprost and timolol. Both of these drugs lower eye pressure.

Latanoprost works by increasing the natural outflow of fluid from inside the eye. Timolol works by decreasing the fluid production in the eye.

**What are the ingredients in XALACOM?**

Medicinal ingredients: Each millilitre (mL) contains 50 micrograms of latanoprost and 5 milligrams of timolol as timolol maleate.

Non-medicinal ingredients: Benzalkonium chloride (preservative), disodium hydrogen phosphate anhydrous, hydrochloric acid, sodium chloride, sodium dihydrogen phosphate monohydrate, sodium hydroxide and water for injection.

**XALACOM comes in the following dosage forms:**

XALACOM is supplied in a 5 mL plastic ophthalmic dispenser bottle with a dropper tip, screw cap and tamper proof overcap.

**Do not use XALACOM if:**

- you have a reactive airway disease including the following:
  - asthma
  - a history of asthma
  - severe chronic obstructive pulmonary disease (a condition where the lungs are inflamed)
- you have heart problems such as:
  - a sinus bradycardia (a condition where there is a low heart beat)
  - sick sinus syndrome (a heart rhythm disorder)
  - sino-atrial block (a condition in which there is a disorder in the normal rhythm of the heart)

- second or third degree atrioventricular block not controlled with pace-maker
- overt cardiac (heart) failure
- cardiogenic shock (a serious condition in which your heart suddenly cannot pump enough blood)

- you are allergic to latanoprost, timolol, benzalkonium chloride, any other ingredient in the product or any part of the container. (See **What are the ingredients in XALACOM?**)

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take XALACOM. Talk about any health conditions or problems you may have, including if you:**

- have heart diseases or conditions such as:
  - chest pain or tightness,
  - breathlessness or choking,
  - heart failure,
  - low blood pressure (hypotension).
- have problems with your blood pressure or thyroid.
- have poor blood circulation disease (a condition called Raynaud's disease or Raynaud's syndrome).
- have diabetes or have low blood sugar levels.
- have or have had muscle weakness or have been diagnosed as having myasthenia gravis (a condition where your muscles are weaker).
- are using any other eye drops or taking any other medication.
- are pregnant, think you might be pregnant or you are planning a pregnancy.
- are breast feeding or planning to breastfeed.
- have or have had herpes simplex keratitis (a condition where the cornea is inflamed. This is caused by the herpes simplex virus)
- have eyes that are sensitive to light
- are planning a surgery
- have kidney or liver disease

**Other warnings you should know about:**

XALACOM is not recommended for use in children.

**Driving and Using Machinery:**

Your sight may become blurred for a short period of time just after using XALACOM. Do NOT drive or use machines until your sight is clear again.

**Surgery:**

If you are planning to have surgery, tell your healthcare professional that you are using XALACOM. XALACOM may change the effects of some medicines used during anaesthesia.

**Contact Lenses:**

XALACOM contains a preservative (benzalkonium chloride) that may be absorbed by contact lenses. The preservative may form a solid with an ingredient (thimerosal) present in many contact lens soaking solutions.

If you wear contact lenses, remove them before using XALACOM. Wait 15 minutes after applying the eye drops before putting your lenses back in.

If you are using more than one type of eye drop medicine, wait at least 5 minutes between each different eye drop

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with XALACOM:**

Tell your healthcare professional if you are using or intend to use medicines to lower blood pressure, heart medicine or medicines to treat diabetes or other medicines including:

- Medicines used to treat blood pressure issues like calcium channel blockers.
- Medicines used to treat heart rhythm conditions like antiarrhythmics such as amiodarone or quinidine.
- Medicines used to treat depression like monoamine oxidase inhibitors, fluoxetine, and paroxetine.
- Medicines used to treat pain like narcotics.
- Medicines used to treat heart conditions like digitalis and beta-adrenergic blocking agents.

XALACOM can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma.

**How to take XALACOM:**

Always use XALACOM exactly as your healthcare professional has told you.

**Usual adult dose:**

1 drop of XALACOM should be dropped into the affected eye(s) once daily.

Do not allow the dropper tip of the bottle to touch the eye or anything else. This could contaminate the tip with common bacteria known to cause eye infections. Serious damage to the eye and loss of vision may result if you use eye drop solutions that have become contaminated.

If you experience any type of eye condition or have surgery, immediately talk to your healthcare professional about continuing to use XALACOM.

**Follow these steps to help you use XALACOM properly:**

1. Wash your hands and sit or stand comfortably. If you wear contact lenses, remove them before using your eye drops.
2. Twist off the outer protective cap from the bottle.



3. Unscrew the inner cap of the bottle.



4. Once the bottle is opened, hold it in one hand and steady your thumb against your brow or the bridge of your nose.
5. Use your index finger to gently pull down the lower eyelid of the affected eye(s) to create a pocket for the drop.



6. Gently press, or lightly tap, the side of the bottle to allow only a single drop to fall into the pocket. Do not let the tip of the bottle touch your eye.
7. Close your eye for 2 to 3 minutes.
8. If your healthcare professional has told you to use drops in both eyes, repeat the process for the other eye. XALACOM should be used until your doctor tells you to stop.

**Overdose:**

If you think you, or a person you are caring for, have taken too much XALACOM contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you forget one dose of XALACOM, continue with the next dose as normal. Do not take two doses to make up for the one that you missed. If you take too many doses, you may irritate your eye.

**What are possible side effects from using XALACOM?**

These are not all the possible side effects you may have when taking XALACOM. If you experience any side effects not listed here, tell your healthcare professional.

- Change in eye colour
- Longer eye lashes
- Iris cysts
- A feeling that something is in your eye
- Eye redness
- Blurred vision
- Skin rash
- Eye pain
- Eye irritation (for example, burning or stinging eyes)
- Eyelid inflammation
- Infection in nose, sinuses and/or throat
- Headache
- Loss of appetite
- Vomiting
- Nausea
- Muscle pain
- Joint pain
- Chest pain
- Fast-beating or fluttering heart beat
- Asthma
- Low blood sugar in diabetics
- Dry eyes
- Anxiety
- Nervousness
- Dizziness
- Confusion
- Disorientation
- Insomnia
- Hallucinations

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **RARE** | | | |
| **Irregular heartbeat** | | | ✓ |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| **Hypertension** (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations. | | | ✓ |
| **Hypotension** (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up). | | | ✓ |
| **Severe respiratory reactions** | | | ✓ |
| **Hypersensitivity** (allergic reactions): swelling of the mouth, and throat, difficulty breathing, hives, itching, rash. | | | ✓ |
| **Muscle weakness**: increased muscle weakness in those with myasthenia gravis or a similar condition. | | | ✓ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

Keep out of reach and sight of children.

Before XALACOM is first opened, keep it in a fridge (between 2°C and 8°C).

Once the bottle has been opened, XALACOM can be kept at normal room temperature up to 25°C.

Protect from light.

XALACOM must be used within 10 weeks after opening the bottle. Discard the bottle and/or unused contents after 10 weeks.

XALACOM should not be used after the expiry date on the bottle.

**If you want more information about XALACOM:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.mylan.ca, or by calling 1-844-596-9526.

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