PRODUCT MONOGRAPH

[Pr]APO-LATANOPROST-TIMOP

Latanoprost 50 mcg/mL and Timolol 5 mg/mL as Timolol Maleate

Ophthalmic Solution

Sterile

Elevated Intraocular Pressure Therapy

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

APOTEX INC.
150 Signet Drive
Toronto Ontario
M9L 1T9

DATE OF REVISION:
August 16, 2018

Control No.: 216591

Table of Contents

[Pr]APO-LATANOPROST-TIMOP

Latanoprost 50 mcg/mL and Timolol 5 mg/mL as Timolol Maleate

Ophthalmic Solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
ophthalmic	fixed combination of latanoprost 50 mcg/ml and timolol 5 mg/ml as timolol maleate	Benzalkonium chloride (preservative), hydrochloric acid, sodium chloride, sodium hydroxide, sodium phosphate dibasic anhydrous, sodium phosphate monobasic monohydrate and water for injection.

INDICATIONS AND CLINICAL USE

APO-LATANOPROST-TIMOP Ophthalmic Solution (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 APO-LATANOPROST-TIMOP Ophthalmic Solution (the combination drug) is considered appropriate.

APO-LATANOPROST-TIMOP Ophthalmic Solution should not be used to initiate therapy.

For details of information obtained from Clinical Trials with latanoprost and timolol maleate, please refer to **CLINICAL TRIALS** section. Also see **DOSAGE AND ADMINISTRATION**.

CONTRAINDICATIONS

APO-LATANOPROST-TIMOP Ophthalmic Solution (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 latanoprost, timolol, benzalkonium chloride or any other ingredient in the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION** and **PACKAGING** section of the product monograph.

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 **CONSUMER 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: APO-LATANOPROST-TIMOP (latanoprost and timolol maleate) may interact with other drugs (see **DRUG INTERACTIONS)**. The effect on intraocular pressure or the known effects of systemic beta-adrenergic blocking agents may be exaggerated when latanoprost and timolol maleate 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 **DOSAGE AND 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, latanoprost and timolol maleate 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.

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

Latanoprost and timolol maleate 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 **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 **ADVERSE REACTIONS).**

Due to the prostaglandin component latanoprost, APO-LATANOPROST-TIMOP should be used with caution in patients with a history of herpetic keratitis. APO-LATANOPROST-TIMOP 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 APO-LATANOPROST-TIMOP. Contact lenses may be reinstalled 15 minutes after administering APO-LATANOPROST-TIMOP.

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. APO-LATANOPROST-TIMOP 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** APO-LATANOPROST-TIMOP**, 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 color 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 color 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: APO-LATANOPROST-TIMOP 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
APO-LATANOPROST-TIMOP has not been studied in patients with renal impairment and therefore should be used with caution in such patients.

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, APO-LATANOPROST-TIMOP 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.

Sexual Function / Reproduction

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.

Special Populations

Pregnant Women: No reproduction toxicity studies have been conducted with latanoprost and timolol maleate. 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 **TOXICOLOGY.**

APO-LATANOPROST-TIMOP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women: 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 latanoprost and timolol maleate in nursing infants, APO-LATANOPROST-TIMOP should be used with caution in nursing women.

Pediatrics: APO-LATANOPROST-TIMOP is not recommended for use in children. The safety and efficacy of the use of APO-LATANOPROST-TIMOP in children has not been established.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug

reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

Latanoprost and timolol maleate 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 latanoprost and timolol maleate 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 1
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		
	Latanoprost and timolol maleate 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)

Body system / preferred term	Number (%) of patients per treatment group		
	Latanoprost and timolol maleate N=394	Latanoprost N=414	Timolol N=415
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 discoloration	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 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		
	Latanoprost and timolol maleate 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)*

Body system / preferred term	Number (%) of patients per treatment group		
	Latanoprost and timolol maleate N=394	Latanoprost N=414	Timolol N=415
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)	(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 to 20% of patients treated with latanoprost and timolol maleate 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.

Post-Market Adverse Drug 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
Eye disorders	Foreign body sensation, macular oedema including cystoid macular oedema, corneal erosion, punctate keratitis, corneal oedema, uveitis, iritis, pseudopemphigoid of ocular conjunctiva, trichiasis, photophobia, 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
General disorders and administration site conditions	Chest pain
Infections and infestations	Herpetic keratitis
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia
Nervous system disorders	Dizziness
Respiratory, thoracic and mediastinal disorders	Acute asthma attacks, asthma aggravation, asthma, dyspnoea
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	Cystoid macular oedema, choroidal detachment (following filtration surgery), corneal erosion, keratitis, diplopia, decreased corneal sensitivity, signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing, redness), dry eyes, ptosis, blepharitis, 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, dyspepsia, nausea
General disorders and administration site conditions	Chest pain, 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
Nervous system disorders	Cerebral vascular accident, cerebral ischemia, dizziness, increase in signs and symptoms of myasthenia gravis, paraesthesia, somnolence, headache, syncope
Psychiatric disorders	Behavioural changes and psychic disturbances including, confusion, hallucinations, anxiety, disorientation, nervousness, depression, insomnia, 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), cough, dyspnoea, nasal congestion
Skin and subcutaneous tissue disorders	Skin rash, 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.

DRUG INTERACTIONS

Drug-Drug Interactions

No specific interaction studies have been performed with latanoprost and timolol maleate.

Patients who are receiving treatment with latanoprost and timolol maleate 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 latanoprost and timolol maleate 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 APO-LATANOPROST-TIMOP. 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 **Drug-Lifestyle Interactions: Use of Contact Lenses)**.

Drug-Lifestyle Interactions

Effects on ability to drive and use of machines: In common with other eye preparations, installation of eye drops may cause transient blurring of vision.

Use of Contact Lenses:

APO-LATANOPROST-TIMOP 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 Drug-Drug Interactions**). Therefore, contact lenses should be removed before installation of the eye drops and may be reinserted after 15 minutes.

DOSAGE AND ADMINISTRATION

The recommended adult (including the elderly) dosage of APO-LATANOPROST-TIMOP Ophthalmic Solution (latanoprost and timolol maleate) is one 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 APO-LATANOPROST-TIMOP Ophthalmic Solution 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 APO-LATANOPROST-TIMOP Ophthalmic Solution once daily. The IOP lowering effect of APO-LATANOPROST-TIMOP Ophthalmic Solution 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 **CLINICAL TRIALS** section.

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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

There is no human data available on overdosage with latanoprost and timolol maleate.

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.

In monkeys latanoprost has been infused intravenously to doses up to 500 mcg/kg without major effects on the cardiovascular system. Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction.

If overdose with latanoprost and timolol maleate occurs, treatment should be symptomatic.

If APO-LATANOPROST-TIMOP Ophthalmic Solution 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

APO-LATANOPROST-TIMOP consists of two components: latanoprost and timolol maleate. Each mL of APO-LATANOPROST-TIMOP 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 APO-LATANOPROST-TIMOP Ophthalmic Solution once daily results in additional intraocular pressure reduction compared to either component administered alone separately. For details of information obtained from Clinical Trials with latanoprost and timolol maleate, please refer to **CLINICAL TRIALS** section.

Pharmacokinetics

Latanoprost: 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 in man indicate that the maximum concentration in the aqueous humor, approximately 30 ng/mL, is reached about 2 hours after topical administration of latanoprost alone. The acid of latanoprost has a plasma clearance of 0.40 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%. 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 in animal studies and are excreted primarily in the urine.

Timolol: 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). The half-life of timolol in plasma is about 6 hours. Timolol is extensively metabolized in the liver. The metabolites, and unchanged timolol, are excreted in the urine.

Latanoprost and timolol maleate: 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

Elderly, Gender, Pediatric and Race: Differences in the pharmacokinetics of latanoprost and timolol maleate in these populations has not been investigated.

Diseases and Demographic Characteristics: No studies have been performed to investigate the influence of other diseases or demographic characteristics on the pharmacokinetics of latanoprost and timolol maleate due to the inherit difficulties in measuring the drug concentrations after topical administration on the eyes.

STORAGE AND STABILITY

Store unopened bottle under refrigeration (2°C to 8°C). Protect from light. Once opened, the bottle may be stored at room temperature from 15°C to 25°C for 10 weeks. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

APO-LATANOPROST-TIMOP Ophthalmic Solution is supplied in a 5 mL white translucent LDPE bottle with a white translucent LDPE dropper and light yellow opaque HDPE cap with sealing tape.

Each bottle contains 2.5 mL of APO-LATANOPROST-TIMOP Ophthalmic Solution corresponding to approximately 80 drops of solution.

APO-LATANOPROST-TIMOP Ophthalmic Solution 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: Benzalkonium chloride (preservative), hydrochloric acid, sodium chloride, sodium hydroxide, sodium phosphate dibasic anhydrous, sodium phosphate monobasic monohydrate and water for injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Latanoprost and timolol ophthalmic solution contains latanoprost and timolol maleate.

Latanoprost:

Common Name: latanoprost

Chemical Name:

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

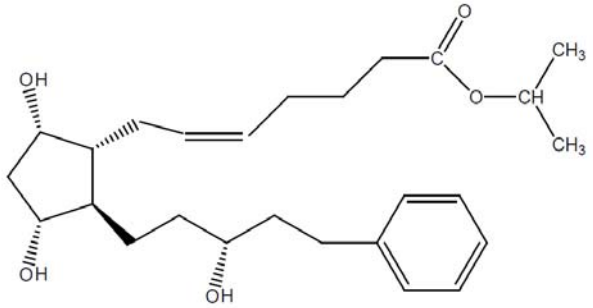
2) 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropyl ester

3) [1*R*-[1α(Z),2β(R),3α,5α]]-7-[3,5-Dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoic acid 1-methylethyl ester

4) 5-Heptenoic acid,7[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl) cyclopentyl]-1-methylethyl ester, [1R-[1α(Z),2β(R*),3α ,5α]]-

Molecular formula and molecular weight: $C_{26}H_{40}O_5$, 432.59 g/mol

Structural Formula:



Physicochemical properties:

Description: Pale yellow to yellow viscous oil.

Solubility: Practically insoluble in water but freely soluble in alcohol, chloroform and acetone.

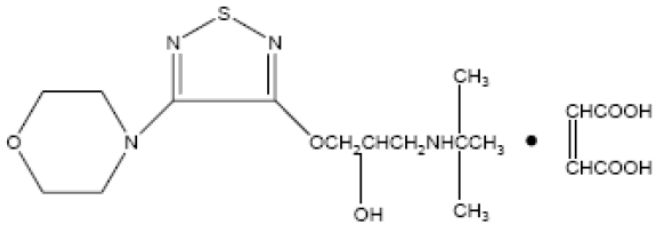
Timolol Maleate

Proper Name: Timolol Maleate USP/EP

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

Molecular formula and molecular weight: $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$, 432.5 g/mol

Structural Formula:



Physicochemical properties:

Description: White, or practically white, crystalline powder.

Solubility: Soluble in water, alcohol and methanol; sparingly soluble in chloroform and propylene glycol; insoluble in ether and cyclohexane.

pH: 3.8 – 4.3 (2% solution in water)

pKa: Timolol base: 9.2 (water at 25°C)

Melting Point: Melts at about 199°C with decomposition

CLINICAL TRIALS

Two 6-month, randomized, double-masked, multicenter clinical studies were conducted to compare the IOP-lowering effect of 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 3 shows the mean diurnal IOP reductions at the end of the treatment latanoprost and timolol maleate (FC) and the individual monotherapies for all patients. All values are statistically significant.

Table 3: Mean diurnal IOP reduction between treatment groups (primary analysis) Analysis of ITT population by repeated measures ANCOVA

Study	Number of patients/ treatment group	Analysis	Difference between treatments (mmHg)
004	FC: 140 Latanoprost: 147 Timolol: 149 Total: 436	FC vs. latanoprost FC vs. timolol	-1.2 -1.9
005	FC: 138 Latanoprost: 140 Timolol: 140 Total: 418	FC vs. latanoprost FC vs. timolol	-1.0 -2.9

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 latanoprost and timolol maleate over the individual monotherapies as shown in Table 4.

Table 4: Responder* rate within each treatment group for each designated threshold value.

Threshold value	Treatment Groups (%)		
	FC N=278	Latanoprost N=287	Timolol 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 latanoprost and timolol maleate (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 mm Hg and 17.1 mm Hg respectively. Results from this short-term crossover study indicates that latanoprost and timolol maleate 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 latanoprost and timolol maleate was maintained during this period.

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

DETAILED PHARMACOLOGY

Human Pharmacodynamics

Latanoprost and timolol maleate 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. Its onset of action is within one hour and maximal effect occurs within 6 to 8 hours.

A randomized, double-masked, parallel-group, single-dose study was performed to compare the IOP reducing effect of latanoprost and timolol maleate ophthalmic solution (latanoprost-timolol) with that of placebo in patients with increased IOP. Administration of a single drop of latanoprost-timolol gave a pronounced IOP reduction after one hour. This corresponds well with the time of onset for timolol, which is 30 minutes after drop installation. The IOP reduction effect was maintained throughout the 12-hour period, with no clear peak effect. A maximum IOP reduction of 12.4 mmHg was obtained at 6.4 hours post-dose. This corresponds with the known peak effect of latanoprost, which is at around 6 to 8 hours after single-dose administration. A clinically and statistically significant IOP reduction was still maintained at 24 and 48 hours after the single-dose administration.

Another study was a repeated-dose, cross-over study in which two 14-day treatment periods were separated by a 4-week washout period. Results showed that when compared with placebo, latanoprost-timolol reduced IOP at all time points during the 24-hour period. The difference in mean IOP between latanoprost-timolol and placebo during 24 hours was statistically significant, and in favor of latanoprost-timolol. Furthermore, no marked peak effect on IOP reduction could be defined, although the mean IOP reduction during the day was found to be more marked than nocturnal IOP reduction. The absence of a marked peak IOP-reducing effect in this study is consistent with results from the single-dose study. Within 2 weeks of the last drop of latanoprost-timolol, the IOP had returned to baseline levels.

Results of the above two studies support that latanoprost-timolol is an effective ocular hypotensive agent in a patient population with diagnosed glaucoma or ocular hypertension. The hypotensive effect is consistent throughout the day, with no marked peak IOP-reducing effect at any single time point.

Human Pharmacokinetics

Systemic pharmacokinetics

One study was designed to evaluate the systemic pharmacokinetics of latanoprost-timolol. After once daily administration of one drop of either timolol or latanoprost-timolol in each eye during five days, the absorption of timolol was rapid but variable. The maximum plasma concentration was somewhat higher and t_{max} was reached earlier after administering timolol alone than after administering latanoprost-timolol. This indicates a less rapid absorption of timolol after administering latanoprost-timolol when compared with giving timolol alone. The mean AUC_{ss} of timolol on day 4 and 5 was 5.1 mcg•h/L for latanoprost-timolol and 5.7 mcg•h/L for timolol ophthalmic solution, respectively. There was no difference in terminal half-life of timolol between treatments. The maximum plasma concentration was reached about 5 minutes after dose and the median C_{max} was 33 pg/mL on day 4 and <30 pg/mL on day 5 after once daily administration of the latanoprost-timolol. No systemic interactions between latanoprost and timolol of any clinical significance were observed in this study.

Ocular pharmacokinetics

A study was designed to evaluate the ocular pharmacokinetics of latanoprost-timolol in cataract surgery patients. After a single-dose administration of 30 mcL of latanoprost-timolol, latanoprost or timolol, the absorption rate of latanoprost and timolol into human aqueous humor was similar in patients receiving the combination therapy or monotherapy. The aqueous humor concentrations of the acid of latanoprost tended to be higher 1 to 4 hours after administration of latanoprost-timolol compared with latanoprost monotherapy. Latanoprost C_{max} after latanoprost-timolol administration was 30 ng/mL compared to 15 ng/mL after giving latanoprost alone. The resulting AUC for latanoprost was 2.4 times higher after latanoprost-timolol administration than after latanoprost administration. These differences were not clinically significant, and could be explained by timolol's mechanism of action in reducing aqueous humor production. The t_{max} and elimination half-life of latanoprost and timolol were similar after administration of latanoprost-timolol, latanoprost or timolol.

No interactions in the ocular pharmacokinetics of any clinical significance was observed after administering latanoprost and timolol in a combination medication compared to administering each drug separately as monotherapy.

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.

Reproduction And Teratology

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.

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.

Other Studies

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.

REFERENCES

1. Zimmerman TJ, Kaufman HE. Timolol dose response and duration of action. Arch Ophthalmol 1977; 95:605-7.

2. Soll DB. Evaluation of timolol in chronic open-angle glaucoma. Once a daily vs. twice a day. Arch Ophthalmol 1980; 98:2178-81.

3. Yalon M, Urinowsky E, Rothkoff L, et al. Frequency of timolol administration. Am J Ophthalmol 1981; 92:526-9.

4. Coakes RL, Brubaker RF. The mechanism of timolol in lowering intraocular pressure in the normal eye. Arch Ophthalmol 1978; 96:2045-8.

5. Neufeld AH. Experimental studies on the mechanism of action of timolol. Surv Ophthalmol 1979; 23:363-70.

6. Mori M, Sakurai M, Araie M. Topical timolol and blood-aqueous barrier permeability to protein in human eyes. Nippon Ganka Gakkai Zasshi 1992; 96:1418-22.

7. Green K, Hatchett TL. Regional ocular blood flow after chronic topical glaucoma drug treatment. Acta Ophthalmol 1987; 65:503-6.

8. Mastropasqua L, Carpineto P, Ciancaglini M, Gallenga PE. A 12-month, randomized, double-masked study comparing latanoprost with timolol in pigmentary glaucoma. Ophthalmology 1999; 106(3):550-5.

9. Stjernschantz J, Selén G, Sjöquist B, Resul B. Preclinical pharmacology of latanoprost, a phenyl-substituted $PGF_{2\alpha}$ analogue, after topical application in normal and ocular hypertensive human eyes. Arch Ophthalmol 1993; 111:1352-58.

10. Lindsey JD, Kashiwagi K, Kashiwagi F, Weinreb RN. Prostaglandins alter extracellular matrix adjacent to human ciliary muscle cells *in vitro*. Invest Ophthalmol Vis Sci 1997; 38:2214-23.

11. Rulo AH, Greve EI, Hoyng PF. The additive hypotensive effect of latanoprost, a prostaglandin $F_{2\alpha}$ analogue, and timolol in patients with elevated intraocular pressure. Br J Ophthalmol 1994; 78:899-902.

12. Alm A, Widengård I, Kjellgren D, Söderström M, et al. Latanoprost administered once daily caused a maintained reduction of intraocular pressure in glaucoma patients treated concomitantly with timolol. Br J Ophthalmology 1995; 79:12-6.

13. Diestelhorst M, Almegård B. Comparison of two fixed combinations of latanoprost and timolol in open-angle glaucoma. Graefe's Arch Clin Exp Ophthalmol 1998; 236: 577-81.

14. Almegard B, Åsenblad –G. A 6-month randomized, double-masked comparison of fixed combination of latanoprost and timolol with the individual components, continuing into a 6-month open label safety study of fixed combination in patients with glaucoma or ocular hypertension. A multicenter study in the United States. Pharmacia & Upjohn Report c0013532, 1999.

15. Backman C, Åsenblad N-G. A 6-month randomized, double-masked comparison of fixed combination of latanoprost and timolol with the individual components, continuing into a 6-month open label safety study of fixed combination in patients with glaucoma or ocular hypertension. A multicenter study in Germany. Pharmacia & Upjohn Report c0013595, 1999.

16. Product Monograph - XALACOM (fixed combination of latanoprost 50 mcg/mL and timolol 5 mg/mL as timolol maleate); Pfizer Canada Inc. Control No. 207642. Date of Revision: September 7, 2017.

PART III: CONSUMER INFORMATION

PrAPO-LATANOPROST-TIMOP

Latanoprost 50 mcg/mL and Timolol 5 mg/mL (as Timolol Maleate) Ophthalmic Solution

This leaflet is part III of a three-part "Product Monograph" published when APO-LATANOPROST-TIMOP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-LATANOPROST-TIMOP. Contact your doctor or pharmacist if you/your child have any questions about the drug. Please read this information carefully.

ABOUT THIS MEDICATION

What APO-LATANOPROST-TIMOP is used for:
APO-LATANOPROST-TIMOP is used to reduce eye pressure in patients with open angle glaucoma ocular hypertension. Both these conditions are related to an increase in pressure within the eye and eventually they may affect your eyesight.

What APO-LATANOPROST-TIMOP does:
APO-LATANOPROST-TIMOP is a combination of an ophthalmic prostaglandin drug *(latanoprost)* and an ophthalmic beta-blocking drug *(timolol)*, both of which lower the pressure within the eye in different ways. The prostaglandin drug works by increasing the natural outflow of fluid from inside the eye. The beta-blocking drug works by decreasing the fluid production in the eye.

When it should not be used:
- **if you have a reactive airway disease including bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease.**
- **if you have heart problems such as a sinus bradycardia (low heart beat), sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker, overt cardiac (heart) failure, or cardiogenic shock.**
- **if you have known hypersensitivity to latanoprost, timolol, benzalkonium chloride or any other ingredient in the product. (See What the medicinal ingredients are).**

What the medicinal ingredient is:
Each millilitre (mL) contains 50 micrograms of latanoprost and 5 milligrams of timolol as timolol maleate

What the non-medicinal ingredients are:
Benzalkonium chloride (preservative), hydrochloric acid, sodium chloride, sodium hydroxide, sodium phosphate dibasic anhydrous, sodium phosphate monobasic monohydrate and water for injection.

What dosage forms it comes in:
APO-LATANOPROST-TIMOP is supplied in a 5 mL plastic bottle with a plastic dropper and plastic cap with sealing tape. Each bottle contains 2.5 mL of APO-LATANOPROST-TIMOP, corresponding to approximately 80 drops of solution.

WARNINGS AND PRECAUTIONS

Before using APO-LATANOPROST-TIMOP, talk to your doctor or pharmacist if:
- You are allergic to any of the ingredients in APO-LATANOPROST-TIMOP.
- You have a respiratory disease such as asthma, have a history of asthma, or have chronic obstructive pulmonary disease (severe lung disease which may cause wheeziness, difficulty in breathing and/or long-standing cough).
- You have disturbances of heart rate such as slow heart beat (bradycardia).
- You have certain heart diseases or conditions – symptoms can include chest pain or tightness, breathlessness or choking, heart failure, low blood pressure (hypotension).
- You have problems with your blood pressure or thyroid function.
- You have poor blood circulation disease (peripheral arterial disease such as Raynaud's disease or Raynaud's syndrome).
- You have diabetes or have low blood sugar levels.
- You have or have had muscle weakness or have been diagnosed as having myasthenia gravis.
- You are using any other eye drops or taking any other medication.
- You are pregnant, think you might be pregnant or you are planning a pregnancy.

- You are breast feeding or planning to breastfeed.
- You have or have had herpes simplex keratitis (inflammation of the cornea caused by the herpes simplex virus
- Your eyes are sensitive to light
- You are planning a surgery
- You have kidney or liver disease

Tell your doctor before you have an operation that you are using APO-LATANOPROST-TIMOP as Timolol Maleate may change effects of some medicines used during anaesthesia.

APO-LATANOPROST-TIMOP contains a preservative (benzalkonium chloride) that may be absorbed by contact lenses. The preservative may form a precipitate with an ingredient (thimerosal) present in several contact lens soaking solutions. If you wear contact lenses, remove them before using APO-LATANOPROST-TIMOP. 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 medication, wait at least 5 minutes between each different eye drop

INTERACTIONS WITH THIS MEDICATION

APO-LATANOPROST-TIMOP can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma. Tell your doctor if you are using or intend to use medicines to lower blood pressure, heart medicine or medicines to treat diabetes or other medicines including:

- calcium channel blockers, beta-adrenergic blocking agent
- antiarrhythmics (e.g. amiodarone, quinidine),
- monoamine oxidase inhibitors
- narcotics
- digitalis, fluoxetine, paroxetine

PROPER USE OF THIS MEDICATION

Always use APO-LATANOPROST-TIMOP exactly as your doctor has told you.

Usual adult dose:

One drop of APO-LATANOPROST-TIMOP should be dropped into the affected eye(s) once daily.

Do not allow the dropper tip of the bottle to touch the eye or other surrounding structures, because this could contaminate the tip with common bacteria known to cause eye infections. Serious damage to the eye with subsequent 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 seek your doctor's advice concerning the continued use of the bottle you are using.

If you forget to use your eye drops at the usual time, wait until it is time for your next dose. If you put too many drops in your eye(s), you may feel some slight irritation.

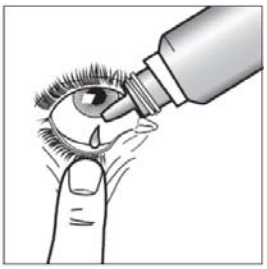
Follow these steps to help you use APO-LATANOPROST-TIMOP properly:

1. Wash your hands and sit or stand comfortably. If you wear contact lenses, remove them before using your eye drops.

2. Unscrew the cap of the bottle.

3. Once the bottle is opened, hold it in one hand and steady your thumb against your brow or the bridge of your nose.

4. Use your index finger to gently pull down the lower eyelid of the affected eye(s) to create a pocket for the drop.



5. 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.

6. Close your eye for 2 to 3 minutes.

7. If your doctor has told you to use drops in both eyes, repeat the process for the other eye.

APO-LATANOPROST-TIMOP should be used until your doctor tells you to stop.

APO-LATANOPROST-TIMOP is not recommended for use in children.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional poison control centre, even if there are no symptoms.

Missed Dose:

If you forget one dose of APO-LATANOPROST-TIMOP, continue with the next dose as normal. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In some patients, APO-LATANOPROST-TIMOP may cause a gradual change in eye color by increasing the amount of brown pigment in the iris (the colored part of the eye). This change may not be noticeable for several months to years. This effect may be more noticeable in patients with eye colors that are mixtures of green and brown, blue/gray and brown, or yellow and brown. The brown pigment may gradually spread outward toward the outside edge of the iris. However, the entire iris or parts of it may become more brownish in appearance. This change may be more noticeable if you are only treating one eye. Therefore, there is the potential for permanent difference in the colour between the treated and the untreated eyes. Your doctor will examine you regularly to make sure that your medication is working and look for changes in eye color. If you should experience any changes in eye color, your doctor can stop treatment. However, any color change that has already occurred may be permanent, even after the medication is stopped.

APO-LATANOPROST-TIMOP may also cause your eye lashes to darken, appear thicker and longer than they usually do. A very small number of people may notice their eye lid skin looks darker after using APO-LATANOPROST-TIMOP for some time. These changes may be more noticeable if you are only treating one eye. APO-LATANOPROST-TIMOP may also cause your eye lashes to become ingrown.

APO-LATANOPROST-TIMOP may cause iris cyst (small cyst appearing in the colored part of the eye).

When using APO-LATANOPROST-TIMOP, you might feel as if there is something in your eye(s). Your eye(s) might water and become red. As with other eye drops, if your vision is blurred when you first put your drops in, wait until this wears off before you drive or operate machinery. A few people using APO-LATANOPROST-TIMOP have developed a skin rash.

A few people may experience changes in their vision, sometimes in combination with a red and sore/painful eye. These changes do not always occur right after administering the drops, and if they occur, you may find that reading and seeing fine details more difficult. Although unlikely, if you experience any of these changes, stop using APO-LATANOPROST-TIMOP and contact your doctor immediately.

APO-LATANOPROST-TIMOP may cause the following side effects as well.

Common side effects: eye irritation, including burning and stinging, inflammation of the eye lid and eye pain, upper respiratory tract infection.

Effects on the body: headache and skin rash, loss of appetite, muscle pain, joint pain, chest pain, heart palpitations, asthma, low blood sugar in diabetics, dry eyes, nervous system effects including anxiety, nervousness, dizziness, confusion, disorientation, insomnia, hallucinations.

Be sure to tell your doctor (or pharmacist) if you notice any other unwanted side effects.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / Effect		Talk with your doctor or pharmacist		Stop taking the drug and seek emergency medical assistance
		Only if severe	In all cases	
Rare	Heart effects such as irregular			√

	heartbeat, high blood pressure and low blood pressure			
	Severe respiratory reactions has been reported with administration of timolol			√
	Allergic reactions with symptoms such as swelling of the mouth, and throat, difficulty breathing, hives, itching, rash.			√
	Beta adrenergic blockers (e.g. timolol) have been reported to cause muscle weakness in those with myasthenia gravis or similar conditions			√

HOW TO STORE IT

Always keep medicine well out of the reach of children.

Before APO-LATANOPROST-TIMOP is first opened, keep it in a fridge (between 2°C and 8°C), out of direct light.

Once the bottle has been opened, APO-LATANOPROST-TIMOP can be kept at normal room temperature from 15°C to 25°C, out of direct light. APO-LATANOPROST-TIMOP must be used within 10 weeks after opening the bottle. Discard the bottle and/or unused contents after 10 weeks. APO-LATANOPROST-TIMOP should not be used after the expiry date on the bottle.

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.

MORE INFORMATION

If you want more information about APO-LATANOPROST-TIMOP:

- 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 http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last revised: August 16, 2018