PRODUCT MONOGRAPH

^{Pr}pms-LATANOPROST-TIMOLOL

Fixed combination of latanoprost 50 mcg/mL and timolol 5 mg/mL as timolol maleate

Sterile Ophthalmic Solution

Elevated Intraocular Pressure Therapy
Prostaglandin $F_{2\alpha}$ analogue and beta-adrenergic receptor blocker

PHARMASCIENCE INC.
6111 Royalmount Avenue, Suite #100,
Montréal, Québec
H4P 2T4

www.pharmascience.com

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Ophthalmic	Fixed combination of latanoprost 50 mcg/mL and timolol 5 mg/mL as timolol maleate	Benzalkonium Chloride (as a preservative), Disodium Hydrogen Phosphate Anhydrous, Hydrochloric Acid (for pH adjustment), Sodium Chloride, Sodium Dihydrogen Phosphate Monohydrate, Sodium Hydroxide (for pH adjustment) and Water for injection.

INDICATIONS AND CLINICAL USE

pms-LATANOPROST-TIMOLOL (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 pms-LATANOPROST-TIMOLOL (the combination drug) is considered appropriate.

pms-LATANOPROST-TIMOLOL should not be used to initiate therapy.

For details of information obtained from Clinical Trials with latanoprost-timolol, please refer to CLINICAL TRIALS section, also see DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

pms-LATANOPROST-TIMOLOL 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: Latanoprost and timolol maleate may interact with other drugs (see r DRUG INTERACTIONS**).** The effect on intraocular pressure or the known effects of systemic beta-adrenergic blocking agents may be exaggerated when pms-LATANOPROST-TIMOLOL 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, pms-LATANOPROST-TIMOLOL 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 have 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, pms-LATANOPROST-TIMOLOL should be used with caution in patients with a history of herpetic keratitis.

pms-LATANOPROST-TIMOLOL 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 pms-LATANOPROST-TIMOLOL. Contact lenses may be reinstalled 15 minutes after administering pms-LATANOPROST-TIMOLOL.

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. pms-LATANOPROST-TIMOLOL 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 pms-LATANOPROST-TIMOLOL, 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: pms-LATANOPROST-TIMOLOL 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

Latanoprost-timolol 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, pms-LATANOPROST-TIMOLOL 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-timolol ophthalmic solution. 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**.**

pms-LATANOPROST-TIMOLOL 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-timolol in nursing infants, pms-LATANOPROST-TIMOLOL should be used with caution in nursing women.

Pediatrics: pms-LATANOPROST-TIMOLOL is not recommended for use in children. The safety and efficacy of the use of latanoprost and timolol maleate ophthalmic solution 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-timolol ophthalmic solution was generally well tolerated. No adverse events specific to latanoprost-timolol ophthalmic solution 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-timolol ophthalmic solution 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-timolol ophthalmic solution 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-timolol 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 pigmentation increased	6 (1.5)	13 (3.1)	4 (1.0)
Iritis	-	1 (0.2)*	2 (0.5)*
Irritation eye	49 (12.4)	54 (13.0)	29 (7.0)
Keratitis	4 (1.0)	3 (0.7)	1 (0.2)
Oedema eyelid	2 (0.5)	4 (1.0)	2 (0.5)
Photophobia	6 (1.5)	1 (0.2)	3 (0.7)
Retinal disorder	1 (0.3)	3 (0.7)	6 (1.4)
Uveitis	1 (0.3)*	-	-
Vision abnormal	26 (6.6)	29 (7.0)	22 (5.3)
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 2: Systemic adverse events (AE) that occurred in ≥1% of patients*, in any of the treatment groups, by body system/preferred term†

	Number (%) of patients per treatment group		
Body system / preferred term	**Latanoprost-timolol 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)	1 (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)*
Hypercholesterolemia	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 16-20% of patients treated with latanoprost-timolol ophthalmic solution 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

- Ocular: foreign body sensation, punctate epithelial erosions, macular edema/cystoid macular edema, iritis/uveitis, corneal edema and erosions; photophobia
- Respiratory: asthma, asthma exacerbation and dyspnea.
- Skin: darkening of the palpebral skin, periorbital and lid changes resulting in deepening of the eyelid sulcus
- Infections and infestations: herpetic keratitis.

Timolol Maleate (topical formulation)

- Special senses: signs and symptoms of ocular irritation (e.g., burning, stinging, itching, tearing, redness), blepharitis, vision blurred, dry eyes, corneal erosion, keratitis, decreased corneal sensitivity, visual disturbances including refractive changes (due to withdrawal of meiotic therapy in some cases), cystoid macular edema, diplopia, ptosis, choroidal detachment (following filtration surgery), tinnitus.
- Cardiovascular: bradycardia, arrhythmia, hypotension, atrioventricular block, cardiac failure, worsening of angina pectoris, syncope, heart block, congestive heart failure, palpitation, cardiac arrest, edema, claudication, Raynaud's phenomenon, cold hands and feet.
- Respiratory: bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, cough, nasal congestion, pulmonary edema.
- Body as a whole: asthenia, fatigue, chest pain.
- Skin: alopecia, skin rash psoriasiform rash or exacerbation of psoriasis, pseudopemphigoid.
- Hypersensitivity: symptoms of allergic reactions including angioedema, urticaria, pruritus, localized and generalized rash.
- Nervous system/psychiatric: cerebral vascular accident, dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, headache, behavioural changes and psychic disturbances including confusion, hallucinations, anxiety, disorientation, nervousness, depression, insomnia, nightmares, memory loss, cerebral ischemia.
- Digestive: nausea, diarrhea, dyspepsia, dry mouth, dysgeusia, vomiting, abdominal pain, retroperitoneal fibrosis.
- Urogenital: decreased libido, impotence, sexual dysfunction, Peyronie's disease.
- Immunologic: systemic lupus erythematosus and myalgia.
- Metabolism and Nutrition Disorders: anorexia, masked symptoms of hypoglycemia in diabetic patients.

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-timolol ophthalmic solution.

Patients who are receiving treatment with pms-LATANOPROST-TIMOLOL 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, antiarrhythmics (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-timolol 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 pms-LATANOPROST-TIMOLOL. 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: pms-LATANOPROST-TIMOLOL 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 pms-LATANOPROST-TIMOLOL (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 pms-LATANOPROST-TIMOLOL 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 pms-LATANOPROST-TIMOLOL once daily. The IOP lowering effect of pms-LATANOPROST-TIMOLOL 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

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 pms-LATANOPROST-TIMOLOL occurs, treatment should be symptomatic.

If pms-LATANOPROST-TIMOLOL 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 suspected drug overdosage, particularly accidental oral ingestion, contact your regional poison control center immediately

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

pms-LATANOPROST-TIMOLOL consists of two components*:* latanoprost and timolol maleate. Each mL of pms-LATANOPROST-TIMOLOL 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 pms-LATANOPROST-TIMOLOL 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-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 drugs that enter 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-timolol
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-timolol 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-timolol ophthalmic solution 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 2.5 mL container may be stored at room temperature up to 25ºC for 10 weeks. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

pms-LATANOPROST-TIMOLOL 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 is added as a preservative. If required, the pH of the solution is adjusted with Hydrochloric Acid and/or Sodium Hydroxide.

pms-LATANOPROST-TIMOLOL (latanoprost and timolol maleate) is a sterile, isotonic, buffered, clear and colorless aqueous solution. One drop contains approximately 1.5 mcg of latanoprost and 150 mcg of timolol. pms-LATANOPROST-TIMOLOL is intended for topical administration on the eye.

pms-LATANOPROST-TIMOLOL is supplied in a 5 mL plastic ophthalmic dispenser bottle with a dropper tip and screw cap.

Each bottle contains 2.5 mL of pms-LATANOPROST-TIMOLOL corresponding to approximately 80 drops of solution.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

pms-LATANOPROST-TIMOLOL contains latanoprost and timolol maleate.

Latanoprost

Proper Name: Latanoprost

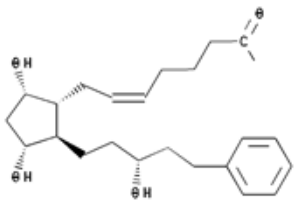
Chemical Names: 1) Isopropyl-(Z)-7{(1R, 2R, 3R, 5S)-3, 5-dihydroxy-2-[(3R)-3-hydroxy-5- phenylpentyl] cyclopentyl}-5-heptenoate

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

Molecular Formula: $C_{26}H_{40}O_5$

Molecular Mass: 432.6 g/mol

Structural Formula:



Physicochemical Properties

Description: Colourless to yellow viscous liquid.

Solubility: Latanoprost was dissolved in various solvents to prepare solutions. Latanoprost is freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol, and octanol and soluble in DMSO, and DMF. It is practically insoluble in water.

Timolol Maleate

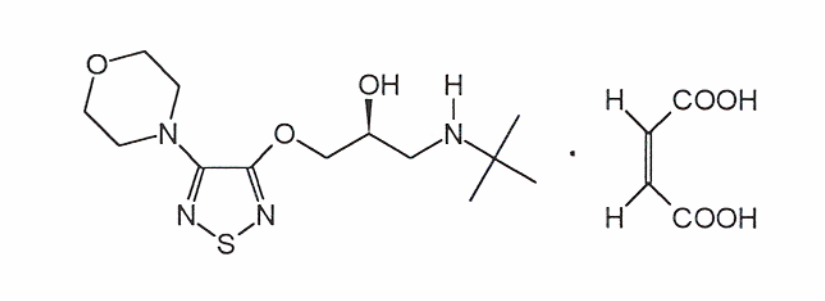
Proper Name: timolol maleate

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

Molecular Formula: $C_{13}H_{24}N_4O_3S \bullet C_4H_4O_4$

Molecular Mass: 432.5 g/mol

Structural Formula:



Physicochemical Properties

Description: 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: 199ºC with decomposition

CLINICAL TRIALS

Two 6-months, randomized, double-masked, multicenter clinical studies were conducted to compare the IOP-lowering effect of latanoprost-timolol ophthalmic solution 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-timolol ophthalmic solution (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-timolol over the individual monotherapies as shown in Table 4.

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

	Treatment Groups (%)		
Threshold value	**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-timolol (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 indicate that latanoprost-timolol 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-timolol 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 tmax 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 AUCs 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 Cmax 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 Cmax 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 (IV) 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.

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16. [pr]XALACOM® Product Monograph-Pfizer Canada Inc., Version July 21, 2014, control number 173378.

PART III: CONSUMER INFORMATION

[pr]pms-LATANOPROST-TIMOLOL
Latanoprost 50 mcg/mL and timolol 5 mg/mL
Ophthalmic solution

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

ABOUT THIS MEDICATION

What the medication is used for:
pms-LATANOPROST-TIMOLOL 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 it does:
pms-LATANOPROST-TIMOLOL 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 pms-LATANOPROST-TIMOLOL 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 milliliter (mL) contains 50 micrograms of Latanoprost and 5 milligrams of Timolol as Timolol Maleate.

What the nonmedicinal ingredients are:
Benzalkonium Chloride (preservative), Sodium Chloride, Sodium Dihydrogen Phosphate Monohydrate, Disodium Hydrogen Phosphate Anhydrous, Water for Injection, Hydrochloric Acid and Sodium Hydroxide

What dosage forms it comes in:
Ophthalmic Solution: 50 mcg/mL Latanoprost and 5 mg/ mL Timolol (as Timolol Maleate)

WARNINGS AND PRECAUTIONS

BEFORE using pms-LATANOPROST-TIMOLOL, talk to your doctor or pharmacist if:

- You are allergic to any of the ingredients in pms-LATANOPROST-TIMOLOL
- 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 pms-LATANOPROST-TIMOLOL as Timolol Maleate may change effects of some medicines used during anaesthesia.

pms-LATANOPROST-TIMOLOL 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 pms-LATANOPROST-TIMOLOL. 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

pms-LATANOPROST-TIMOLOL 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 pms-LATANOPROST-TIMOLOL exactly as your doctor has told you.

Usual adult dose:
One drop of pms-LATANOPROST-TIMOLOL 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 pms-LATANOPROST-TIMOLOL 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 inner 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.
   pms-LATANOPROST-TIMOLOL should be used until your doctor tells you to stop.

pms-LATANOPROST-TIMOLOL is not recommended for use in children.

Overdose:

In case of drug overdose, particularly accidental oral ingestion, contact a health care practitioner, hospital emergency department or regional Poison Control Center immediately, even if there are no symptoms.

Missed Dose:
If you forget one dose of pms-LATANOPROST-TIMOLOL, continue with the next dose as normal. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In some patients, pms-LATANOPROST-TIMOLOL 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.

pms-LATANOPROST-TIMOLOL 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 pms-LATANOPROST-TIMOLOL for some time. These changes may be more noticeable if you are only treating one eye.

When using pms-LATANOPROST-TIMOLOL, 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 latanoprost and timolol maleate 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 pms-LATANOPROST-TIMOLOL and contact your doctor immediately.

Latanoprost and timolol maleate 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, sore muscles, 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 drug and seek immediate emergency medical attention
		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 and sight of children.

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

Once the bottle has been opened, pms-LATANOPROST-TIMOLOL can be kept at normal room temperature up to 25°C, out of direct light.

pms-LATANOPROST-TIMOLOL must be used within 10 weeks after opening the bottle.

Discard the bottle and/or unused contents after 10 weeks.

pms-LATANOPROST-TIMOLOL 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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Pharmascience Inc. at 1-888-550-6060.

This leaflet was prepared by
Pharmascience Inc.
Montreal, Canada
H4P 2T4

www.pharmascience.com

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