PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **Sandoz Timolol**

Timolol Maleate Ophthalmic Solution

Solution, 0.25%, 0.5% w/v timolol (as timolol maleate), ophthalmic

USP

Antiglaucoma Preparations and Miotics

Sandoz Canada Inc.

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RECENT MAJOR LABEL CHANGES

6 Dosage Forms, Strengths, Composition and Packaging	03/2024

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Sandoz Timolol is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with:

- Chronic open glaucoma.
- Ocular hypertension.
- Aphakic patients with glaucoma, including those wearing contact lenses.
- Narrow angles and a history of spontaneous or iatrogenically-induced narrow-angle closure in the opposite eye in whom reduction of IOP is necessary (see 7 WARNINGS AND PRECAUTIONS, ophthalmologic).

1.1 Pediatrics

Sandoz Timolol is not recommended for use in children or adolescents. The safety and effectiveness of Sandoz Timolol in pediatric patients < 18 years of age have not been established.

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

1.2 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

Sandoz Timolol is contraindicated in patients with:

- Hypersensitivity to timolol or any ingredient in the formulation or component of the container (see 6 Dosage forms, Strengths, Composition and Packaging).
- Hypersensitivity to other beta-blockers.
- Bronchospasm, including bronchial asthma, a history of bronchial asthma, or chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sinoatrial block, second and third degree atrioventricular block, overt cardiac failure, or cardiogenic shock.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Sandoz Timolol

When a patient is transferred from another topical ophthalmic beta-adrenergic blocking agent, that agent should be discontinued after proper dosing on one day and treatment with Sandoz Timolol

started on the following day with 1 drop of 0.25% Sandoz Timolol in the affected eye(s) twice a day. The dose may be increased to 1 drop of 0.5% Sandoz Timolol twice a day if the clinical response is not adequate.

When a patient is transferred from a single anti-glaucoma agent, other than a topical ophthalmic beta-adrenergic blocking agent, continue the agent already being used and add one drop of 0.25% Sandoz Timolol in each affected eye(s) twice a day. On the following day, discontinue the previously used anti-glaucoma agent completely and continue with Sandoz Timolol. If a higher dosage of Sandoz Timolol is required, substitute one drop of 0.5% solution in each affected eye(s) twice a day.

When a patient is transferred from several concomitantly administered anti-glaucoma agents, individualization is required. The physician may be able to discontinue some or all of the other anti-glaucoma agents. Adjustments should involve one agent at a time.

4.2 Recommended Dose and Dosage Adjustment

Sandoz Timolol

The recommended starting dosage is one drop of 0.25% solution in the affected eye(s) twice a day.

If clinical response is not adequate, the dosage may be changed to one drop of 0.5% solution in each affected eye(s) twice a day. If the patient's IOP is still not at a satisfactory level on this regimen, concomitant therapy with miotics, epinephrine and systemically administered carbonic anhydrase inhibitors may be instituted with Sandoz Timolol. Other topically applied medications should be administered at interval of not less than 10 minutes.

Since in some patients the IOP-lowering response to Sandoz Timolol Solution may require a few weeks to stabilize, evaluation should include a determination of IOP after approximately 4 weeks of treatment with Sandoz Timolol.

If IOP is maintained at satisfactory levels, the dosage schedule may be changed to one drop a day in the affected eye(s). Because of naturally occurring diurnal variations in IOP, satisfactory response to the once-a-day dose is best determined by measuring IOP at different times during the day.

4.4 Administration

Nasolacrimal occlusion or gently closing the eyelid for 2 minutes after instillation is recommended. This may reduce the systemic absorption of medications administered via the ocular route and result in a decrease in systemic adverse events.

To avoid contamination, patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. The contents should not be used for more than one month after the date on which the container is first opened.

If using another eye medication, use it at least 10 minutes before or after the use of Sandoz Timolol.

4.5 Missed Dose

Patients who miss a dose, should be advised to apply it as soon as possible. However, if it is almost time for the next dose, patients are advised to skip the missed dose and go back to regular dosing schedule to avoid doubling the dose.

5 OVERDOSAGE

No data are available in regard to overdosage in humans.

The most common signs and symptoms to be expected with overdosage with administration of a systemic beta-adrenergic receptor blocking agent are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure.

The following therapeutic measures should be considered:

1) Gastric lavage: if ingested.
2) Symptomatic bradycardia: use atropine sulfate intravenously in a dosage of 0.25 mg to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.
3) Hypotension: use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or levarterenol. In refractory cases the use of glucagon hydrochloride has been reported to be useful.
4) Bronchospasm: use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.
5) Acute cardiac failure: conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed if necessary by glucagon hydrochloride which has been reported to be useful.
6) Heart block (second or third degree): use isoproterenol hydrochloride or a transvenous cardiac pacemaker.]

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Ophthalmic	Solution of timolol maleate in two dosage strengths: 0.25% and 0.5%. Each mL of Sandoz Timolol 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of Sandoz Timolol 0.5% contains 5.0 mg of timolol (6.8 mg of timolol maleate)	Contains 0.01% Benzalkonium chloride as preservative, monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and purified water.

Sandoz Timolol is a sterile, clear, isotonic, buffered, colourless to pale yellow aqueous solution. Sandoz Timolol, 0.5%, is supplied in 5 mL and 10 mL white, opaque, plastic ophthalmic DROP-TAINER* dispensers with a controlled drop tip, and the 0.25% is supplied in 10 mL.

7 WARNINGS AND PRECAUTIONS

General

FOR TOPICAL OPHTHALMIC USE ONLY.

Sandoz Timolol contain timolol, a beta-adrenergic blocking agent. As with other topically applied ophthalmic agents, timolol may be absorbed systemically. The same types of cardiovascular, pulmonary and other adverse reactions reported with systemic beta-adrenergic blocking agents may occur with topical ophthalmic administration.

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or in 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. They may also mask the signs of hyperthyroidism.

Beta-adrenergic blocking agents have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms, such as diplopia, ptosis and generalized weakness.

The effect on IOP or the known effects of systemic beta-blockade may be potentiated when Sandoz Timolol is given to patients already receiving an oral beta-adrenergic blocking agent. The response of these patients should be closely observed. The use of two local beta-adrenergic blocking agents is not recommended.

Cardiovascular

Cardiac reactions, and rarely, death in association with cardiac failure, have been reported following administration of timolol maleate.

Sandoz Timolol is not recommended for use in patients with cardiovascular diseases (e.g., coronary heart disease, Prinzmetal's angina, and cardiac failure) and hypotension, as it can cause worsening of Prinzmetal's angina, severe peripheral and central nervous system disorders, and hypotension. Therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and for adverse reactions.

Caution is advised when using Sandoz Timolol in patients with severe peripheral circulatory disturbances/disorders, such as severe forms of Raynaud's disease or Raynaud's syndrome.

Drug Interactions

Mydriasis resulting from concomitant use of ophthalmic beta-blockers, such as timolol, and adrenaline (epinephrine) has been reported occasionally.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic solutions with beta-blockers, such as timolol, are administered concomitantly with oral calcium channel blockers, quinidine, catecholamine-depleting drugs, beta-adrenergic blocking agents, antiarrhythmics (e.g. amiodarone, digitalis glycosides or parasympathomimetics).

Potentiated systemic beta-blockade (e.g. decreased heart rage) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, cimetidine, fluoxetine, paroxetine) and timolol.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-adrenergic blocking agents.

Driving and Operating Machinery

Sandoz Timolol may cause temporary blurred vision or other visual disturbances that can affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

Immune

Anaphylactic Reactions: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge to such allergens, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions. In such cases, alternatives to epinephrine should be considered.

Ophthalmologic

In patients with angle-closure glaucoma, the immediate objective of treatment is to re-open the angle. This requires constricting the pupil with a miotic. Sandoz Timolol have little or no effect on the pupil. When Sandoz Timolol is used to reduce elevated intraocular pressure in angle-closure glaucoma, they should be used with a miotic and not alone.

As with the use of other anti-glaucoma drugs, diminished responsiveness to Sandoz Timolol after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least three years, no significant difference in mean IOP has been observed after initial stabilization.

Sandoz Timolol contains the preservative benzalkonium chloride, which may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to instillation of Sandoz Timolol and wait at least 15 minutes after dosing before re-inserting contact lenses.

Benzalkonium chloride has also been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Close monitoring is required with frequent or prolonged use.

Choroidal detachment has been reported with administration of aqueous suppression therapy (e.g., timolol, acetazolamide) after filtration procedures.

Peri-Operative Considerations

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects, such as that of adrenaline. The anesthesiologist should be informed if and when patients are receiving timolol.

Reproductive Health: Female and Male Potential

- **Function**

Sexual Function/Reproduction: There are no data on the effect of timolol on human fertility.

Respiratory

Respiratory reactions, including death due to bronchospasm in patients with asthma, have been reported following administration of timolol maleate.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. Epidemiological studies have not revealed malformative effects, but show a risk of intrauterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g., bradycardia, hypotension, respiratory distress and hypoglycemia) have been observed in the neonate when beta-blockers have been administered until delivery. Sandoz Timolol should not be used during pregnancy unless clearly necessary. If Sandoz Timolol is administered until delivery, the neonate should be carefully monitored during the first days of life.

7.1.2 Breast-feeding

Sandoz Timolol should not be used by nursing women. Beta-blockers are excreted in breast milk, having the potential to cause serious undesirable effects in the breastfeeding infant.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In clinical studies with timolol ophthalmic solution, the most common ocular adverse reactions reported were ocular hyperemia (5.1%) and eye irritation (2.4%). Other ocular adverse reactions occurring with a frequency of at least 1% were eye pain, ocular discomfort, and vision blurred.

Timolol ophthalmic solution is usually well tolerated.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, 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 reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2- Treatment-Related Adverse Reactions

MedDRA SOC and PT (version 15.1)	Frequency Category	Pooled Total (N=2632)	
		N	%
Eye disorders			
Ocular hyperemia	Common	133	5.05

MedDRA SOC and PT (version 15.1)	Frequency Category	Pooled Total (N=2632)	
		N	%
Eye irritation	Common	63	2.39
Eye pain	Common	40	1.52
Ocular discomfort (including foreign body sensation in eyes and abnormal sensation in eyes)	Common	34	1.29
Vision blurred	Common	32	1.22

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions with timolol ophthalmic solution (<1%):

Cardiac disorders: bradycardia, myocardial infarction

Eye disorders: corneal erosion, punctate keratitis, keratitis, iritis, conjunctivitis, blepharitis, reduced visual acuity (including ptosis and refractive changes due to withdrawal of miotic therapy in some cases), photophobia, dry eye, lacrimation increased, eye discharge, eye pruritus, eyelid margin crusting, anterior chamber inflammation, eyelid edema, conjunctival hyperemia, uveitis, diplopia, asthenopia, eczema of eyelids, erythema of eyelid, eyelid pruritus, conjunctival edema, corneal pigmentation

Gastrointestinal disorders: dysgeusia, dyspepsia, abdominal discomfort, dry mouth

General disorders and administration site conditions: fatigue, asthenia, chest discomfort

Nervous system disorders: headache, cerebral ischemia, dizziness, migraine

Psychiatric disorders: depression

Respiratory, thoracic and mediastinal disorders: asthma, bronchitis, dyspnea, chronic obstructive pulmonary disease, bronchospasm, cough, wheezing, nasal congestion

Skin and subcutaneous tissue disorders: swelling face, erythema

Vascular disorders: hypotension, blood pressure increased, edema peripheral, peripheral coldness

Causal Relationship Unknown*:*

The following adverse reactions have been reported but a causal relationship to therapy with timolol ophthalmic solution has not been established: anorexia, aphakic cystoid, CNS effects (e.g., anxiety, confusion, disorientation, hallucinations, nervousness, somnolence and other psychic disturbances), dry mouth, dyspepsia, hypertension, macular edema, nasal congestion, and retroperitoneal fibrosis.

Adverse reactions reported in clinical experience with oral timolol may be considered potential side effects of ophthalmic timolol.

8.5 Post-Market Adverse Reactions

Eye disorders: choroidal detachment (following filtration surgery), eyelid ptosis.

Cardiac disorders: cardiac arrest, atrioventricular block (complete, lower degree or aggravation), arrhythmia, palpitations.

Gastrointestinal disorders: vomiting, diarrhea, nausea.

Immune system disorders: angioedema, hypersensitivity.

Metabolism and nutrition disorders: hypoglycemia.

Musculoskeletal and connective tissue disorders: arthropathy.

Nervous system disorders: cerebrovascular accident, syncope, paresthesia.

Psychiatric disorders: insomnia, amnesia, nightmares.

Reproductive system and breast disorders: sexual dysfunction.

Skin and subcutaneous tissue disorders: urticaria, psoriasis, rash, alopecia.

Vascular disorders: Raynaud's phenomenon.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

The following may interact with Sandoz Timolol:

- Adrenaline (epinephrine) (used to treat life-threatening allergic reactions).
- A group of medicines called oral calcium channel blockers such as diltiazem, verapamil.
- A group of medicines called Catecholamine-depleting drugs (e.g. reserpine).
- Beta-adrenergic blocking agents commonly referred to as beta-blockers such as atenolol, labetalol, metoprolol, nadolol, propranolol, sotalol.
- Medications used to treat certain type of abnormal heart rhythm such as amiodarone, digoxin, quinidine.
- Clonidine (a medication used to treat high blood pressure). Do not stop taking clonidine without talking to healthcare professional.
- Cimetidine (a medication used to treat stomach problem), Fluoxetine and paroxetine [both medications are used to treat depression (low blood mood)]

9.3 Drug-Behavioural Interactions

Not available at the time of initial authorization.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Timolol maleate is a general beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant or local anesthetic (membrane-stabilizing) activity.

Timolol ophthalmic solution, when applied topically in the eye, has the action of reducing elevated as well as normal IOP, whether or not associated with glaucoma. Elevated IOP is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of IOP, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

The onset of reduction in IOP following administration of timolol ophthalmic solution can usually be detected within 30 minutes after a single dose. The maximum effect usually occurs in one to two hours. Significant lowering of IOP has been maintained for periods as long as 24 hours with 0.25% or 0.5% timolol ophthalmic solution twice a day . Repeated observations indicate that the IOP-lowering effect of timolol ophthalmic solution is well maintained over study periods of three years and one year, respectively.

The precise mechanism of the ocular hypotensive action of timolol ophthalmic solution is not clearly established at this time. Tonography and fluorophotometry studies in man suggest that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. Unlike miotics, timolol ophthalmic solution reduces IOP with little or no effect on accommodation or pupil size. These changes in visual acuity due to increased accommodation are uncommon, and dim or blurred vision and night blindness produced by miotics are not evident. In addition, in patients with cataracts the inability to see around lenticular opacities when the pupil is constricted by miotics is avoided.

10.2 Pharmacodynamics

In clinical studies, timolol ophthalmic solution was generally well tolerated and produced fewer and less severe side effects than either pilocarpine or epinephrine.

As with the use of other anti-glaucoma drugs, diminished responsiveness to Sandoz Timolol after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least three years, no significant difference in mean IOP has been observed after initial stabilization.

Timolol ophthalmic solution has also been used in patients with glaucoma wearing conventional (polymethylmethacrylate) hard contact lenses, and has generally been well tolerated. timolol ophthalmic solution has not been studied in patients wearing lenses made with materials other than polymethylmethacrylate.

Unlike miotics, timolol ophthalmic solution reduce IOP with little or no effect on accommodation or pupil size.

10.3 Pharmacokinetics

Not available at the time of initial authorization.

11 STORAGE, STABILITY AND DISPOSAL

Protect from light. Keep out of the reach and sight of children.

Sandoz Timolol: Store at room temperature (15^{o} C - 30^{o} C).

The contents of Sandoz Timolol should not be used for more than one month after the date on which the container is first opened.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

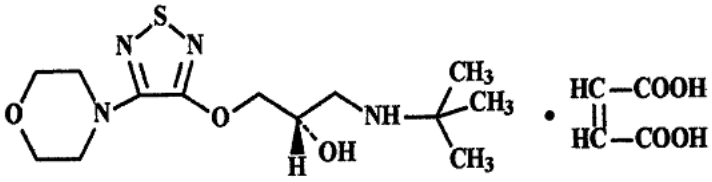
Drug Substance

Proper name: Timolol Maleate

Chemical name: (-)-1-(tert-butyl amino)-3-[(4-morpholino)-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol maleate (1:1) salt

Molecular formula and molecular mass: $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$, 432.49

Structural formula:



Physicochemical properties:

Melting Point: 201.5 - 202.5°C

pKa: 9.2

pH: approximately 4 in a 2% aqueous solution

Physical Description: White, odourless, crystalline powder which is soluble in water, methanol, and alcohol.

14 CLINICAL TRIALS

Not available at the time of initial authorization.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Ocular Effects

No adverse ocular effects were observed in rabbits and dogs administered Timolol Maleate Ophthalmic Solution topically in studies lasting one and two years respectively.

Acute Toxicity (LD_{50})

Species and Age	Sex	Route of Administration	LD_{50} (mg/kg)
Mouse (A)	F	Oral	1 190
	F	Intravenous	222
	F	Subcutaneous	1 040
Rat (YA)	M	Oral	947
	F	Oral	900
	M	Oral (fed)	1 800
	M	Intraperitoneal	390
	F	Intraperitoneal	383
Rat (W)	M	Oral	1 040
	F	Oral	969
	M/F	Intraperitoneal	409
Rat (I)	M/F	Oral	241
	M/F	Subcutaneous	143
Rabbit (A)	M/F	Oral	485
	M/F	Subcutaneous	34
(A) = Adult		(YA) = Young Adult	
(W) = Weanling	(I) = Infant		

Signs of toxicity occurred immediately after intravenous administration and from 10 to 30 minutes following oral, intraperitoneal or subcutaneous administration. The signs observed included lacrimation, ataxia, tremors and bradypnea. Clonic convulsions usually preceded death.

Oral Interaction Studies

Oral acute interaction studies in mice in which timolol maleate was administered with probenecid, methyldopa, hydralazine, hydrochlorothiazide, or tolbutamide, showed that these drugs had no effect on the toxicity of timolol maleate. Timolol maleate had no effect on hypoprothrombinemia induced by bishydroxycoumarin in the dog.

Subacute Toxicity

In rats treated with 100 to 400 mg/kg for seven weeks, excessive salivation seen 5 to 10 minutes after dosing has a dose related incidence in the first week of the study. At necropsy, organ weight studies revealed a significant increase in the kidneys, spleen and liver of some treated animals. Except for splenic congestion, there were no morphological changes to account for the increase in organ weights. Rats treated with 1 gram per day for eight weeks exhibited ptylamism, muscle tremors and transient pale extremities.

In dogs, doses of 200 mg/kg or higher, were lethal to some animals. Low grade tubular nephrosis and trace amounts of hyaline casts in the collecting and convoluted tubules occurred in one of two dogs administered 100 mg/kg/day and in both dogs receiving 400 mg/kg/day. Small foci of tubular degeneration and regeneration occurred in the nephrotic areas. Similar slight multi focal degeneration of the collecting tubules in the medulla of both kidneys was evident in one of four dogs in a 15-day intravenous toxicity study.

Chronic Toxicity

Rats: Timolol was administered orally to rats at dose levels 5, 10 and 25 mg/kg/day for up to 67 weeks. No physical signs, ocular signs or deaths which could be attributed to the drug were evident.

Dogs: In a 54 week oral study, timolol was administered at doses of 5, 10 and 25 mg/kg/day. Body weight and food consumption were normal and no physical signs attributable to treatment were evident. Slight focal hyperplasia of the transitional epithelium was seen in the renal pelvis of one dog receiving 25 mg/kg/day.

Carcinogenicity: Lifetime studies with timolol have been completed in rats at oral doses of 25, 100 and 300 mg/kg/day and in mice at oral doses of 5, 50 and 500 mg/kg/day. In male and female rats and in male mice at all dose levels, and in female mice at dose levels of 5 and 50 mg/kg/day, timolol demonstrated no carcinogenic effect. There was a slight increase in the incidence of mammary adenocarcinomas in female mice that received 500 mg/kg/day (about 500 times the maximum recommended human oral dose, on a mg/kg/day basis). Timolol caused dose-related elevations of serum prolactin in female mice at doses of 100 mg/kg or more, but only very slight transient elevations were found in male mice at does of 500 mg/kg. Since numerous studies have demonstrated that drugs which cause elevations if serum prolactin are associated with mammary tumours in rodents, the mammary tumours in the female mice in the highest dosage group of this study were considered to have resulted from an increased serum prolactin. In humans, no such association between serum prolactin and mammary carcinoma has been established. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

Mutagenicity: Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse and the Micronucleus test and Ctyogenic assay (dose up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 µg/mL). In Ames tests, the high test concentrations of timolol employed, 5 000 or 10 000 µg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA 100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA 100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion of a positive Ames Test.

Reproductive and Teratology: Teratogenic studies in the mouse and rabbit at dose levels of 2 to 50 mg/kg/day did not reveal evidence of teratogenicity but did suggest embryotoxicity at the highest dose. Oral administration of timolol maleate to rats at dose levels of 4 to 100 mg/kg/day did not adversely affect the fertility of male or female rats, their reproductive performance, or the development of their offspring.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] Sandoz Timolol

Timolol Maleate Ophthalmic Solution

(0.25%, 0.5% w/v)

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

What is Sandoz Timolol used for?

Sandoz Timolol is prescription eyes medications. They are used to lower high eye pressure in adults with glaucoma or other eyes diseases (e.g., ocular hypertension).

How does Sandoz Timolol work?

Sandoz Timolol is a brand name. Sandoz Timolol contains the active ingredient timolol maleate. Timolol maleate belong to a class of medication called beta-blockers. It lowers eye pressure by causing the eye to make less fluid.

What are the ingredients in Sandoz Timolol?

Medicinal ingredients: Sandoz Timolol contains the active ingredient timolol maleate. It is available in the following two strengths:

- Sandoz Timolol 0.25% - each mL contains 2.5 mg of timolol (as timolol maleate).
- Sandoz Timolol 0.5% - each mL contains 5.0 mg of timolol (as timolol maleate).

Non-medicinal ingredients: Benzalkonium chloride 0.01% (preservative), monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and purified water.

Sandoz Timolol comes in the following dosage forms:

Sandoz Timolol, 0.5% or 0.25% comes as a solution (liquid) to use as eye drops.

Sandoz Timolol, 0.5% is supplied in 5 mL and 10 mL bottle designed to deliver a precise quantity of the medication. Sandoz Timolol, 0.25% is supplied in a similar 10mL bottle.

Do not use Sandoz Timolol if:

- if you are allergic to:

- timolol or any ingredient in Sandoz Timolol (see What are the ingredients in Sandoz Timolol?).
- if you are allergic to any other beta-blockers such as atenolol, betaxolol, labetalol, levobunolol, metoprolol, nadolol, propranolol, sotalol.

- if you have or have had lung diseases or breathing problems such as asthma, chronic obstructive pulmonary disease (COPD).
- if you suffer from certain heart disease, such as a slow heart rate, an irregular heartbeat, or heart failure.

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

- have or have had diabetes or other blood sugar problems. Timolol may mask signs of low blood sugar;
- have or have had thyroid problems;
- have or have had diseases that causes weakness in your muscles. Beta-blockers have been reported to increase muscle weakness in some patients;
- have or have had heart diseases such as:
  - coronary heart disease (narrowing of the small blood vessels that supply blood and oxygen to the heart causing chest pain or discomfort when you do certain activities);
  - heart failure (weak heart);
  - low blood pressure, heartbeat that is not normal, or a very slow heartbeat.
- have or have had lung or breathing problems (e.g., asthma, chronic obstructive lung disease);
- have or have had blood circulation problems such as Raynaud's syndrome;
- have allergic problems such as eczema, hives or hay fever;
- have allergies to any other medications, foods or any other substances such as preservatives or dyes;
- wear contact lenses.;
- are already using another beta-blocker eye drop. It is not recommended to use two beta-blocker eye drops at the same time;
- have or have had eye problems;
- are pregnant or planning to become pregnant;
- are breast feeding or planning to breast feed.

Other warnings you should know about:

While you are using Sandoz Timolol

- **Driving and using machines:** Sandoz Timolol may cause temporary blurred vision after using the drops. Make sure that your vision is clear before driving a car or operating machinery.
- **If you wear contact lenses**:
    - Sandoz Timolol contains a preservative (benzalkonium chloride) which may cause eye irritation and discolour soft contact lenses. If you wear contact lenses, remove them before using Sandoz Timolol. Wait at least 15 minutes after using Sandoz Timolol to put your lenses back in.
- **If you are planning a surgery**. Timolol may change effects of some medicines used during anaesthesia. Anaesthesia is a treatment with certain medicines so that you do not feel pain during surgery.
- If you have an eye injury, or develop an eye infection while using Sandoz Timolol eye drops, tell your healthcare professional.

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

The following may interact with Sandoz Timolol:

- Adrenaline (epinephrine) (used to treat life-threatening allergic reactions).
- A group of medicines called oral calcium channel blockers such as diltiazem, verapamil.
- A group of medicines called Catecholamine-depleting drugs (e.g. reserpine).
- Beta-adrenergic blocking agents commonly referred to as beta-blockers such as atenolol, labetalol, metoprolol, nadolol, propranolol, sotalol.
- Medications used to treat certain type of abnormal heart rhythm such as amiodarone, digoxin, quinidine.
- Clonidine (a medication used to treat high blood pressure). Do not stop taking clonidine without talking to your healthcare professional.
- Cimetidine (a medication used to treat stomach problem), Fluoxetine and paroxetine [both medications are used to treat depression (low blood mood)]. Ask your healthcare professional if you are not sure if any of your medicines are listed above.

This is not a list of all drugs that interact with Sandoz Timolol.

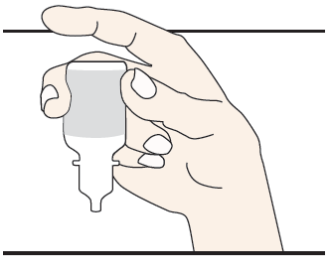
Always keep a list of your medicines and show it to your healthcare professional when you get a new medicine. It is important that your healthcare professional reviews all medications and supplements you are taking before prescribing Sandoz Timolol.

How to take Sandoz Timolol:

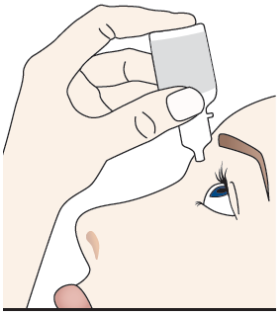
1- Wash your hands before use. Remove contact lenses before using eye drops.

2- Twist the cap off, being careful not to touch the dropper tip.

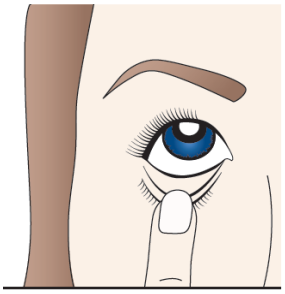
3- Hold the bottle between the thumb and middle finger.



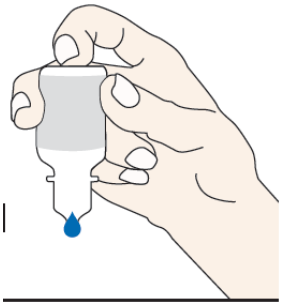
4- Tilt head back.



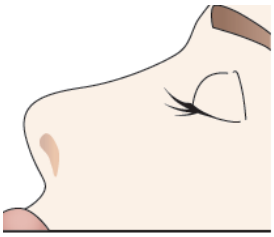
5- Pull the lower eyelid down to form a pocket below the eye.



6- Gently press on the base of the bottle to release one drop. Do not squeeze the bottle.



7- Close the eye for 2 or 3 minutes. If a drop misses the eye, try again.



8- Repeat steps 3 to 7 for the other eye if required.

9- After use, immediately put the cap back on the bottle and keep tightly closed when not in use.

- Be careful not to touch the dropper tip against your eye, eyelid or anything else to avoid contaminating the eye drops.
- If you are using another eye medication, use it at least 10 minutes before or after you use Sandoz Timolol.

Usual dose:

Instill one drop in the affected eye(s) twice a day.

Follow the directions on your prescription label carefully, and ask your healthcare professional to explain any part you do not understand.

Use Sandoz Timolol exactly as directed. Do not start, stop, or change the dose of any drug without checking with your healthcare professional.

Overdose:

If you use too many drops, you may feel light-headed or dizzy, you may faint, have a very slow pulse rate, or have wheezing or difficulty breathing.

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

Missed Dose:

Use Sandoz Timolol at the same time of day. If you miss a dose, apply it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule. Do not double dose.

What are possible side effects from using Sandoz Timolol?

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

- Stomach or bowel problems:
    - Nausea and vomiting
    - Dry mouth
    - Discomfort in the upper belly or abdomen
    - Change in taste
- Problems with your eye/s such as:
    - Blurred vision
    - Burning and stinging
    - Dry eyes
    - Pain in the eye
    - Conjunctivitis (pink eye)
    - Itching and redness of the eye
    - Feeling of having something in the eye,
    - Bleparitis (eyelids problem with signs such as irritated, itchy, reddened and swollen eyelids with dandruff-like debris builds up at the base of the eyelashes)
    - Visual changes (e.g. double visions)
    - Watery eyes
- Changes in the way your hands and feet feel such as:
    - Raynaud's phenomenon
        - cold fingers or toes
        - colour change (white, blue then red) in fingers when exposed to the cold or stress
        - numbness or tingling in the fingers or toes
- Paresthesia: abnormal sensation such as burning or prickling sensation that is usually felt in the hands or feet, but can also occur in other parts of the body
- Difficulty thinking or working because of:
    - Headache
    - Tiredness, weakness
    - Difficulty sleeping, nightmares
    - Changes in mood such as depression, memory loss
- Hair loss or thinning
- Less desire for sex

- Skin rash

Call your healthcare professional or get medical help if any of the side effects listed above bother you or do not go away.

These are not all the possible side effects you may feel when taking Sandoz Timolol . If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
dizziness and light-headedness, which may be due to low blood pressure		✓	
swelling of the hands, feet, ankles or legs		✓	
Breathing problems: • wheezing, difficulty in breathing • shortness of breath			✓
Heart problems: • feelings that your heart is skipping a beat or beating too hard or too fast Raynaud's phenomenon palpitations) • feeling dizzy or confused, • have trouble breathing, • think you may faint, • have pain or tightness in your chest			✓
Allergic reactions: • swelling of the face, lips, mouth, tongue or and throat which may cause difficulty in breathing or swallowing			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
• wheezing, difficulty in breathing, shortness of breath • hives, severe itching and rash			

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

Reporting Side Effects

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

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

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

Storage:

- Keep Sandoz Timolol :
  - away from direct light.
  - out of the reach and sight of children.
- Sandoz Timolol: Store at room temperature (15° C - 30° C).
- Write the date on the bottle when you open the eye drops and throw out any remaining solution one month after opening the bottle. The best way to dispose of your medication is through a medicine take-back program. Check with your pharmacist about how to throw out unused medicines.
- Do not use Sandoz Timolol after the expiry date on the bottle.

If you want more information about Sandoz Timolol:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sandoz.ca, or by calling1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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