PRODUCT MONOGRAPH

PrODAN-TIMOLOL

timolol maleate ophthalmic solution, USP
0.25%, 0.5% w/v timolol

Sterile Ophthalmic Solution

Elevated Intraocular Pressure Therapy

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Solution / 0.25% w/v, 0.5% w/v timolol	*For a complete listing see DOSAGE FORMS, COMPOSITION AND*

INDICATIONS AND CLINICAL USE

ODAN-TIMOLOL (timolol maleate ophthalmic solution, USP) is indicated for the reduction of elevated intraocular pressure.

In clinical trials timolol maleate has been shown to reduce intraocular pressure in:

- Patients with chronic open-angle glaucoma
- Patients with ocular hypertension
- Aphakic patients having glaucoma, including those wearing contact lenses
- Patients with narrow angles and a history of spontaneous or iatrogenically-induced narrow- angle closure in the opposite eye in whom reduction of intraocular pressure is necessary (see WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

- Hypersensitivity to any component of this product. For a complete listing of components see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.

- Sinus bradycardia; sick sinus syndrome; sino-atrial block; second-and third-degree atrioventricular block; overt cardiac failure; cardiogenic shock.

WARNINGS AND PRECAUTIONS

General

As with other topically applied ophthalmic drugs, this drug 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 administration.

Cardiovascular

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered.

Cardiac failure should be adequately controlled before beginning therapy with ODAN-TIMOLOL. Patients with a history of cardiovascular disease, including cardiac failure, should be watched for signs of deterioration of these diseases, and pulse rates should be checked.

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

Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failure, have been reported following administration of timolol maleate ophthalmic solutions.

Because of the potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patient with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with ODAN-TIMOLOL, alternative therapy should be considered.

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

Endocrine and Metabolism

Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus

ODAN-TIMOLOL should be used 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.

Masking of Thyrotoxicosis

β-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of β-adrenergic blocking agents which might precipitate a thyroid storm.

Immune

Risk from Anaphylactic Reaction

While taking beta blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens, either accidental, diagnostic, or therapeutic. These patients may be unresponsive to treatment of anaphylactic reactions with the usual doses of epinephrine since timolol may blunt the beta agonist effect of epinephrine. In such cases, alternatives to epinephrine should be considered.

Ophthalmologic

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol maleate has little or no effect on the pupil. When ODAN-TIMOLOL is used to reduce elevated intraocular pressure in angle-

closure glaucoma they should be used with a miotic and not alone.

Choroidal Detachment
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g., timolol, acetazolamide or combination) after filtration procedures. Management of eyes with chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously.

As with the use of other antiglaucoma drugs, diminished responsiveness to timolol maleate after prolonged therapy has been reported in some patients. However, in clinical studies in which 164 patients have been followed for at least 3 years, no significant difference in mean intra ocular pressure has been observed after initial stabilization.

Contact Lenses
The preservative in ODAN-TIMOLOL is benzalkonium chloride. This preservative is a quaternary ammonium compound that may be absorbed by soft contact lenses. Therefore, ODAN-TIMOLOL should not be administered while wearing soft contact lenses. The contact lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

Neurologic
Muscle Weakness
β-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.

Peri-Operative Considerations
Major Surgery
The necessity or desirability of withdrawal of β-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures.

β-blocking ophthalmological preparations may block systemic β-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving ODAN-TIMOLOL. Some patients receiving beta-adrenergic blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic blocking agents. If necessary during surgery, the effects of β-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

Respiratory
In patients with mild/moderate chronic obstructive pulmonary disease (COPD), ODAN-TIMOLOL should be used with caution, and only if the potential benefit outweighs the potential risk.

Special Populations

Pregnant Women:

Timolol maleate has not been studied in human pregnancy. The use of ODAN-TIMOLOL requires that the anticipated benefit be weighed against possible hazards.

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.

Nursing Women:

Timolol is detectable in human milk. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics:

Safety and effectiveness in children have 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.

Timolol maleate is usually well tolerated.

Like other topically applied ophthalmic drugs, Timolol maleate is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic betablocking agents. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

The following adverse reactions have been reported with ocular administration of this or other timolol maleate formulations, either in clinical trials or since the drug has been marketed.

Body as a Whole

Headache, asthenia, fatigue.

Cardiovascular

Aggravation or precipitation of certain cardiovascular pulmonary and other disorders presumably related to effects of systemic beta blockade has been reported (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS). These include bradycardia, chest pain, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischemia, palpitation, atrioventricular block, cardiac arrest, cardiac failure, congestive heart failure, edema, claudication, Raynaud's phenomenon, cold hands and feet and in insulin-dependent diabetics masked symptoms of hypoglycemia have been reported rarely.

Digestive

Dysgeusia, nausea, diarrhea, dyspepsia, dry mouth, abdominal pain, vomiting.

Hypersensitivity
Signs and symptoms of allergic reactions including anaphylaxis, angioedema, pruritus, urticaria, localized and generalized rash.

Immunologic
Systemic lupus erythematosus.

Integumentary
Alopecia, psoriasiform rash or exacerbation of psoriasis.

Metabolism and Nutrition Disorders
Hypoglycemia.

Musculoskeletal
Myalgia.

Nervous System/Psychiatric
Depression, insomnia, nightmares, memory loss, increases in signs and symptoms of myasthenia gravis, dizziness, paresthesia.

Respiratory
Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, cough.

Special Senses
Signs and symptoms of ocular irritation: including burning and stinging, itching, tearing, redness, conjunctivitis, conjunctival injection, blepharitis, keratitis, blurred vision, decreased corneal sensitivity, and dry eyes. Visual disturbances: including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, corneal erosion ptosis, and choroidal detachment following filtration surgery (see WARNINGS AND PRECAUTIONS), tinnitus.

Urogenital
Decreased libido, Peyronie's disease, sexual dysfunction.

Causal Relationship Unknown
The following adverse reactions have been reported but a causal relationship to therapy with timolol maleate has not been established: aphakic cystoid macular edema, nasal congestion, anorexia, CNS effects (e.g., behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances), hypertension, retroperitoneal fibrosis and pseudopemphigoid.

Potential Adverse Reactions
Adverse reactions reported in clinical experience with systemic timolol maleate may be considered potential side effects of ophthalmic timolol maleate.

DRUG INTERACTIONS

Drug-Drug Interactions

Beta-Adrenergic Blockers

Patients who are already receiving a beta blocker systemically and who are given timolol maleate should be observed for a potential additive effect on the intraocular pressure or on the known systemic effects of beta blockers (hypotension and/or bradycardia). The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium Channel Blockers or Catecholamine-Depleting Drugs

The potential exists for additive effects and production of hypotension and/or marked bradycardia when ODAN-TIMOLOL is administered together with an oral calcium channel blocker or beta-adrenergic blocking agents, catecholamine-depleting drugs such as reserpine, antiarrhythmics, digitalis glycosides, parasympathomimetics or guanethidine.

Clonidine

Oral β-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the β-adrenergic blocking agent should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by β-blocker therapy, the introduction of β-adrenergic blocking agents should be delayed for several days after clonidine administration has stopped.

Epinephrine

Although timolol maleate used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with timolol maleate ophthalmic solutions and epinephrine has been reported occasionally.

Quinidine

Potentiated systemic beta blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, SSRIs) and timolol.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Clinically important changes in standard laboratory parameters were rarely associated with the administration of systemic timolol maleate. Slight increases in blood urea nitrogen, serum potassium, serum uric acid and triglycerides and slight decreases in hemoglobin, hematocrit, and HDL-cholesterol occurred, but were not progressive or associated with clinical manifestations.

No specific drug interaction studies have been performed with timolol maleate.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The dosage is one drop of 0.25% solution in each affected eye twice a day; if the response is inadequate the dosage may be changed to one drop of 0.5% solution twice a day.

If needed, concomitant therapy with other agent(s) for lowering intraocular pressure may be given with ODAN-TIMOLOL. The use of two topical beta-adrenergic blocking agents is not recommended (see WARNINGS AND PRECAUTIONS).

Since in some patients the pressure-lowering response to ODAN-TIMOLOL may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with ODAN-TIMOLOL.

If the intraocular pressure is maintained at satisfactory levels, many patients can be placed on once-a-day therapy. Because of naturally occurring diurnal variations in intraocular pressure, satisfactory response is best determined by measuring the intraocular pressure at different times during the day.

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

How to Transfer Patients from Other Therapy

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 ODAN-TIMOLOL started on the following day with one drop of ODAN-TIMOLOL in the affected eye(s) twice a day.

When a patient is transferred from a single antiglaucoma agent, other than a topical ophthalmic beta-adrenergic blocking agent, continue the agent already being used and add one drop of ODAN-TIMOLOL in each affected eye twice a day. On the following day, discontinue the previously used antiglaucoma agent completely and continue with ODAN-TIMOLOL.

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

Clinical trials have shown the addition of timolol maleate to be useful in patients who respond inadequately to the maximum tolerable antiglaucoma drug therapy.

Missed Dose

If a dose is missed, it should be applied as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the next dose should be taken as usual.

OVERDOSAGE

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

There have been reports of inadvertent overdosage with timolol maleate resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

The following additional therapeutic measures should be considered:

Gastric lavage: If ingested. Studies have shown that timolol does not dialyze readily.

Symptomatic bradycardia: Use atropine sulfate intravenously in a dosage of 0.25 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.

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.

Bronchospasm: Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.

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.

Heart block (second- or third-degree): Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

ACTION AND CLINICAL PHARMACOLOGY

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 maleate combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic receptors by catecholamines having beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of the agonist, which will restore the usual biologic response.

Pharmacokinetics

Timolol maleate (S(-) enantiomer) is significantly metabolized after oral and ophthalmic administration. The drug and the metabolites (hydroxyethylamino, hydroxyethylglycolamino

derivatives and a third minor metabolite that results from the hydroxylation of a terminal methyl group on the tertiary butylamino moiety) are excreted primarily via the kidney. Based on correlation with debrisoquine metabolism, timolol metabolism is mediated primarily by cytochrome P-450 2D6. Timolol is moderately (<60%) bound to plasma proteins.

In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice-daily topical administration of timolol maleate ophthalmic solution 0.5% for 8 days. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.

By comparison to plasma concentrations (10 to 20 ng/mL) following oral 5 mg dose, it was estimated that timolol was approximately 50% bio-available systemically following intraocular administration.

STORAGE AND STABILITY

Store at room temperature (15°-30°C). Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ODAN-TIMOLOL is supplied as a sterile, isotonic, buffered, aqueous solution.

Each mL of ODAN-TIMOLOL 0.25% w/v contains 2.5 mg of timolol (3.4 mg of timolol maleate).

Each mL of ODAN-TIMOLOL 0.50% w/v contains 5.0 mg of timolol (6.8 mg of timolol maleate).

Non-medicinal ingredients: monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and water for injection. Benzalkonium chloride 0.01% is added as preservative.

ODAN-TIMOLOL is a clear, colourless to light yellow solution, supplied in opaque high-density polyethylene ophthalmic bottle with a controlled drop tip.

Ophthalmic Solution ODAN-TIMOLOL equivalent to 2.5 mg (0.25% w/v) timolol per mL, in 5 mL, 10 mL and 15 mL bottles; and Ophthalmic Solution ODAN-TIMOLOL equivalent to 5 mg (0.5% w/v) timolol per mL, in 5 mL, 10 mL and 15 mL bottles.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

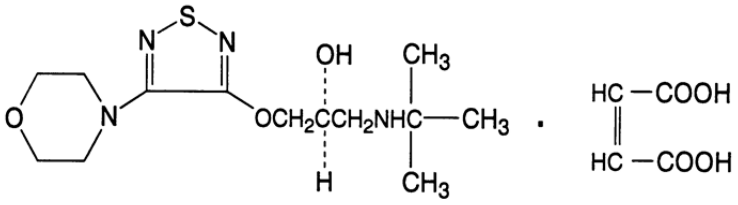
Proper name: Timolol maleate

Chemical name: (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (*Z*)-2- butenedioate(1:1) (salt)

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

Molecular mass: 432.49

Structural formula:



Physicochemical properties: Timolol maleate is a beta-adrenergic receptor blocking agent. It possesses an asymmetric carbon atom in its structure and is provided as the levo isomer. It is a white odourless, crystalline powder which is soluble in water, methanol and alcohol.

CLINICAL TRIALS

Timolol maleate was generally well tolerated and produced fewer and less severe side effects than either pilocarpine or epinephrine. Bradycardia was reported with Timolol maleate(see WARNINGS AND PRECAUTIONS). At trough (12 hours post-dose), the mean reduction was 3.6 beats/minute. At two hours post-dose, the mean reduction in heart rate was 5 beats/minute.

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

DETAILED PHARMACOLOGY

Timolol maleate reduces elevated and normal intraocular pressure whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

Onset of action of timolol maleate is usually rapid, occurring approximately 20 minutes after topical application on the eye. Maximum reduction of intraocular pressure occurs in one to two hours. Significant lowering of intraocular pressure has been maintained for as long as 24 hours with timolol maleate 0.25% or 0.5% Ophthalmic Solution twice a day. Repeated observations over a period of three years indicate that the intraocular pressure-lowering effect of timolol maleate is well maintained.

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

The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate 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 maleate reduces intraocular pressure with little or no effect on accommodation or pupil size. Thus, 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. When changing patients from miotics to timolol maleate a refraction might be necessary when these effects of the miotic have passed.

TOXICOLOGY

Ocular Effects

No adverse ocular effects were observed in rabbits and dogs administered timolol maleate 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	1190
	F	Intravenous	222
	F	Subcutaneous	1040
Rat (YA)	M	Oral	947
	F	Oral	900
	M	Oral (Fed)	1800
	M	Intraperitoneal	390
	F	Intraperitoneal	383
Rat (W)	M	Oral	1040
	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 Interactions 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 influence on the toxicity of timolol maleate. Timolol maleate had no effect on the hypoprothrombinemia induced by bishydroxycoumarin in the dog.

Subacute Toxicity

In rats treated with 100 to 400 mg/kg/day for seven weeks, excessive salivation seen 5 to 10 minutes after dosing had 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 ptyalism, muscle tremors and transient pale extremities.

In dogs, doses of 200 mg/kg/day 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 of 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.

Tumorigenic Tests

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 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 basis). Timolol caused dose-related elevations of serum prolactin in female mice at doses of 100 mg/kg/day or more, but only very slight transient elevations were found in male mice at doses of 500 mg/kg/day. Since numerous studies have demonstrated that drugs which cause elevations of serum prolactin are associated with mammary tumors in rodents, the mammary tumors 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.

Reproductive Studies

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.

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PART III: CONSUMER INFORMATION

PrODAN-TIMOLOL
timolol maleate ophthalmic solution, USP

This leaflet is part III of a three-part "Product Monograph" published when ODAN-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 ODAN-TIMOLOL. Contact your physician or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ODAN-TIMOLOL is the brand name for the medication timolol maleate ophthalmic solution available **only on prescription** through your physician. ODAN-TIMOLOL is an ophthalmic solution of a beta-blocking drug which lowers the pressure in the eye for conditions such as glaucoma and ocular hypertension and is only available through a prescription by your physician.

Remember - This medicine is prescribed for the particular condition that you have. **Do not give this medicine to other persons, nor use it for any other condition.**

What it does:
The active ingredient timolol maleate is a beta-blocking drug. It helps lower the pressure in the eye.

When it should not be used:
Do not use ODAN-TIMOLOL if you:

- are allergic to any of its components (see What the nonmedicinal ingredients are section below);
- have now or have had in the past certain serious breathing problems such as asthma;
- have chronic obstructive lung disease;
- have certain heart diseases or conditions (such as slow or irregular heartbeats);
- are breast feeding or intend to breast feed.

What the medicinal ingredient is:
Timolol maleate

What the nonmedicinal ingredients are:
Monobasic and dibasic sodium phosphate, sodium hydroxide, and water for injection. Benzalkonium chloride is added as a preservative.

What dosage forms it comes in:
ODAN-TIMOLOL (timolol maleate) ophthalmic solution is a sterile eye drop. Each mL contains 2.5mg or 5mg timolol, available in plastic dropper bottles of 5 ml, 10 mL and 15 mL.

WARNINGS AND PRECAUTIONS

This medicine may not be suitable for some patients. So, tell your physician if you think **any** of the following applies to you:

- If you have any medical problems now or have had any in the past, especially asthma and other lung problems or heart problems.
- If you have any allergies to any medications.
- ODAN-TIMOLOL contains benzalkonium chloride as a preservative. This preservative may be absorbed by soft contact lenses. If you wear soft contact lenses, consult your physician before using ODAN-TIMOLOL. Do not administer while wearing (soft) contact lenses. Remove lenses before application and reinsert no earlier than 15 minutes after use.
- If you have now or have had in the past, thyroid problems.
- If you have now or have had in the past, heart problems (such as coronary heart disease, heart failure or low blood pressure).
- If you have now or have had in the past, heart rate disturbances (such as slow or irregular heartbeats).
- If you have or have had in the past, poor blood circulation problems (such as Raynaud's syndrome).
- If you have or have had in the past, lung or breathing problems (such as asthma or chronic obstructive lung disease).
- If you have or have had in the past, diabetes or other blood sugar problems.
- If you are planning major surgery, including eye surgery, as using ODAN-TIMOLOL may change the effects of some medicines during anesthesia.
- If you had past eye problems such as choroidal detachment.
- If you had problems or develop problems with blood flow to the brain.
- If you are pregnant or intend to become pregnant.
- If you are breast feeding or intend to breast feed. Timolol has been detected in human breast milk. Discuss with your physician.

ODAN-TIMOLOL IS NOT RECOMMENDED FOR CHILDREN.

INTERACTIONS WITH THIS MEDICATION

Your physician also needs to know about drugs (including eye drops) that you are using or plan to use, including drugs obtained without a prescription. This is particularly important if you are taking medicine to lower blood pressure or to treat heart disease, diabetes or depression including beta-blockers such as atenolol, epinephrine, quinidine, calcium channel blockers or catecholamine depleting drugs such as reserpine.

No specific drug interaction studies have been done for ODAN-TIMOLOL

PROPER USE OF THIS MEDICATION

Read the following information carefully. **If you need any explanations, or further information, ask your physician or pharmacist.**

- Do not start taking any other medicines unless you have discussed the matter with your physician or pharmacist.
- If you suspect that ODAN- TIMOLOL is causing an allergic reaction (for example, skin rash or redness and itching of the eye), stop its use and contact your physician as soon as possible.
- If you develop any eye irritation or any new eye problems such as redness of the eye or swelling of the eyelids, contact your physician immediately.
- If you are using ODAN- TIMOLOL with another eye drop, the drops should be instilled at least 10 minutes apart.
- Do not change the dosage of the drug without consulting your physician. If you must stop treatment, contact your physician immediately.
- Do not allow the tip of the container to touch the eye or areas around the eye. It may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision. To avoid possible contamination of the container, keep the tip of the container away from contact with any surface.
- Contact your physician without delay if you have ocular surgery or develop a condition that was not present at the time this medication was prescribed (eg. trauma, an infection, etc.).

Usual Adult dose:
The appropriate dosage and duration of treatment will be established by your physician.

The usual dose is one drop in the affected eye(s) in the morning and in the evening.

Overdose:

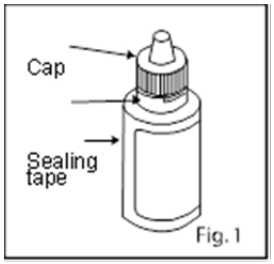
In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you put too many drops in your eye or swallow the contents of the bottle, you should contact your physician immediately.

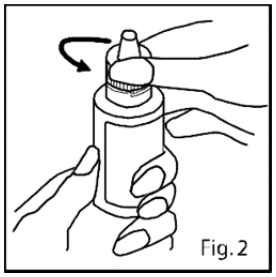
Missed dose:
It is important to apply ODAN- TIMOLOL as prescribed by your by your physician. If you miss a dose, apply it as soon as possible.
However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule. Do not double dose.

INSTRUCTIONS FOR USE

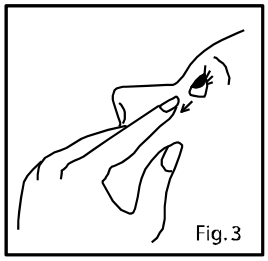
1. Before using the medications for the first time, be sure the plastic sealing tape between the bottle and the cap is unbroken (Fig.1).



2. To break the seal and open the bottle, unscrew the cap by turning as indicated by the arrow (Fig. 2).



3. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye (Fig. 3).



4. Invert the bottle, and press lightly (as shown in Fig.4) until a single drop is dispensed into the eye as directed by your doctor

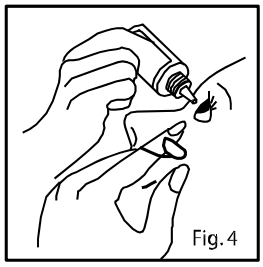


Fig. 4

DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.

Ophthalmic medications, if handled improperly, can become contaminated by common bacteria known to cause eye infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated ophthalmic medications. If you think your medication may be contaminated, or if you develop an eye infection, contact your physician immediately concerning continued use of this bottle.

5. After using ODAN- TIMOLOL, press a finger into the corner of your eye, by the nose (as shown) for 2 minutes. This helps keep ODAN- TIMOLOL in your eye.

6. Repeat steps 3 to 5 with the other eye if instructed to do so by your physician.

7. Replace the cap by turning until it is firmly touching the bottle. Do not overtighten the cap.

8. After you have used all doses, there will be some ODAN-TIMOLOL left in the bottle. You should not be concerned since an extra amount of ODAN- TIMOLOL has been added and you will get the full amount of ODAN-TIMOLOL that your physician prescribed. Do not attempt to remove excess medicine from the bottle.

9. Tell your physician if you wear contact lenses. Depending on the type of lense, your physician may advise that you re-insert your contact lenses not earlier than 15 minutes after application of ODAN- TIMOLOL.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- Any medicine may have unintended or undesirable effects, so-called side effects. Although not all of these side effects may occur, if they do occur, you may need medical attention.
- You may experience muscle pain; abdominal pain; nausea; vomiting; eye symptoms such as burning and stinging, dry eyes, redness of the eye, foreign body sensation or visual changes, such as double vision.
- Other side effects may also occur rarely, and some of these may be serious. These may include shortness of breath.
- ODAN- TIMOLOL has been reported rarely to increase muscle weakness in some patients with myasthenia gravis.
- Your physician or pharmacist has a complete list of the possible side effects from this medication. Please tell your physician or pharmacist promptly about any unusual symptom.
- There are side effects of ODAN- TIMOLOL that may affect some patients' ability to drive and use machines.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your physician or		Stop taking drug and call your physician or pharmacist
		Only if severe	In all cases	
Uncommon	slow heartbeat			✓
Rare	Heart effects such as irregular heartbeat, heart block, low blood pressure			✓
	Allergic reactions with symptoms such as swelling of the mouth and throat, shortness of breath, hives, severe itching and rash			✓

This is not a complete list of side effects. For any unexpected effects while taking ODAN-TIMOLOL, contact your physician or pharmacist.

HOW TO STORE IT

Store at room temperature 15°-30°C. Protect from light.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **-Fax toll-free to 1-866-678-6789, or**
  - **-Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. 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 the sponsor, Odan Laboratories Ltd at:

1-800-387-9342
or
www.odanlab.com

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