PRODUCT MONOGRAPH

PrVAN-Dorzolamide-Timolol

Dorzolamide and timolol eye drops
BP

20 mg/ml, 5 mg/ml
(as dorzolamide hydrochloride and timolol maleate)

Elevated Intraocular Pressure Therapy
(Topical Carbonic Anhydrase Inhibitor and Topical Beta-Adrenergic Blocking Agent)

Manufacturer and Distributor:

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Solution/ each mL contains dorzolamide 20 mg and timolol 5 mg	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

VAN-Dorzolamide-Timolol (dorzolamide and timolol eye drops) is indicated in the treatment of elevated intraocular pressure (IOP) in patients with:

- ocular hypertension
- open-angle glaucoma

when concomitant therapy is appropriate.

CONTRAINDICATIONS

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

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

Sinus bradycardia, sino-atrial block, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock.

Dorzolamide and timolol eye drops have not been studied in patients with severe renal impairment (CrCl < 0.5 mL/s). Because dorzolamide hydrochloride and its metabolite are excreted predominantly by the kidney, VAN-Dorzolamide-Timolol (dorzolamide and timolol eye drops) is not recommended in such patients.

There is a potential for an additive effect with the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and topical carbonic anhydrase

inhibitors concomitantly. The concomitant administration of dorzolamide

hydrochloride and timolol maleate and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

WARNINGS AND PRECAUTIONS

General

As with other topically-applied ophthalmic agents, the active substances may be absorbed systemically. Dorzolamide is a sulfonamide and timolol is a beta-blocker. Therefore, the same types of adverse reactions found with systemic administration of sulfonamides or beta-blockers may occur with topical administration, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation.

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Dorzolamide and timolol eye drops has not been studied in patients with acute angle-closure glaucoma.

Cardiovascular

Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning therapy with VAN-Dorzolamide-Timolol (dorzolamide and timolol eye drops). Patients with a history of cardiac 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 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 solution.

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

Beta-adrenergic blocking agents should be administered with caution in patients subject 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.

Masking of Thyrotoxicosis

Beta-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 beta-adrenergic blocking agents which might precipitate a thyroid storm.

Hepatic

Dorzolamide and timolol eye drops has not been studied in patients with hepatic impairment and therefore should be used with caution in such patients.

Immune

Immunology and Hypersensitivity

In clinical studies, local ocular adverse effects, primarily conjunctivitis and eyelid reactions, were reported with chronic administration of dorzolamide hydrochloride ophthalmic solution. Some of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of drug therapy. Similar reactions have been reported with dorzolamide and timolol eye drops. If such reactions are observed, discontinuation of treatment with VAN-Dorzolamide-Timolol should be considered.

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 accidental, diagnostic, or therapeutic repeated challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Neurologic

Muscle Weakness

Beta-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.

Cerebrovascular Insufficiency

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with VAN-Dorzolamide-Timolol, alternative therapy should be considered.

Ophthalmologic

Corneal Edema

There is an increased risk of developing irreversible corneal edema in a subset of glaucoma patients with endothelial abnormalities including cellular density and/or morphology. In this group of patients evaluation of the cornea, with particular attention to the corneal endothelium, is recommended prior and during treatment with VAN-Dorzolamide-Timolol.

Corneal Edema and Irreversible Corneal Decompensation

Corneal edema and irreversible corneal decompensation has been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery while using dorzolamide. VAN-Dorzolamide-Timolol should be used with caution in such patients.

Contact Lenses

VAN-Dorzolamide-Timolol contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses; therefore, VAN-Dorzolamide-Timolol should not be administered while wearing these lenses. The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

Choroidal Detachment
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g., timolol, acetazolamide) 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.

Peri-Operative Considerations
Surgical Anesthesia
The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol (see OVERDOSAGE).

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

Special Populations
Pregnant Women:
There are no adequate and well-controlled studies in pregnant women. VAN-Dorzolamide-Timolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women:
It is not known whether dorzolamide hydrochloride is excreted in human milk. Timolol maleate does appear in human milk. Because of the potential for serious adverse reactions on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

In a study of dorzolamide hydrochloride in lactating rats, decreases in body weight gain of 5 to 7% in offspring at an oral dose of 7.5 mg/kg/day (94 times the maximum recommended human ophthalmic dose) were seen during lactation. A slight delay in postnatal development (incisor eruption, vaginal canalization and eye openings), secondary to lower fetal body weight, was noted at 7.5 mg/kg/day (94 times the maximum recommended human ophthalmic dose).

Pediatrics:
Safety and effectiveness in children have not been established.

Geriatrics (> 65 years of age):
Of the total number of patients in clinical studies of dorzolamide and timolol eye drops, 49% were 65 years of age and over, while 13% were 75 years of age and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Monitoring and Laboratory Tests
Dorzolamide and timolol eye drops were not associated with clinically meaningful electrolyte disturbances.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions that have been seen with one of the components and may be potential adverse reactions of VAN-Dorzolamide-Timolol are:

Dorzolamide Hydrochloride

Headache; eyelid inflammation; eyelid crusting; eyelid irritation; asthenia/fatigue; iridocyclitis; rash; dizziness; paraesthesia; superficial punctate keratitis, transient myopia (which resolved upon discontinuation of therapy); signs and symptoms of local reactions including palpebral reactions and systemic allergic reactions including angioedema, bronchospasm, urticaria, epistaxis and pruritus; throat irritation, dry mouth.

Timolol Maleate (topical formulation)

Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, and decreased corneal sensitivity, dry eyes; visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, and ptosis; choroidal detachment following filtration surgery, tinnitus; 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; arrhythmia; hypotension; syncope; heart block; cerebrovascular accident; cerebral ischemia; palpitation; cardiac arrest, edema, claudication, Raynaud's phenomenon, cold hands and feet; congestive heart failure, and in insulin-dependent diabetics masked symptoms of hypoglycemia have been reported rarely. In clinical trials, slight reduction of the resting heart rate in some patients; bronchospasm (predominantly in patients with pre-existing bronchospastic disease); cough; headache; asthenia; fatigue; chest pain; alopecia; psoriasiform rash or exacerbation of psoriasis; signs and symptoms of allergic reactions including anaphylaxis angioedema, urticaria, localized and generalized rash; dizziness; increase in signs and symptoms of myasthenia gravis; insomnia; nightmares; memory loss; paresthesia; diarrhea, dyspepsia, dry mouth; abdominal pain; decreased libido, Peyronie's disease; sexual dysfunction; systemic lupus erythematous; myalgia.

Timolol Maleate (systemic formulation)

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

Clinical Trial Adverse Drug Reactions

In clinical studies, dorzolamide and timolol eye drops were generally well tolerated; no adverse experiences peculiar to this combination drug have been observed. Adverse experiences have been limited to those that were reported previously with dorzolamide hydrochloride and/or timolol maleate. In general, common adverse experiences were mild and did not cause discontinuation.

During clinical studies of up to 15 months duration, 1035 patients were treated with dorzolamide and timolol eye drops. Approximately 2.4% of all patients discontinued therapy with dorzolamide and timolol eye drops because of local ocular adverse reactions. Approximately 1.2% of all patients discontinued because of local adverse reactions suggestive of allergy or hypersensitivity.

The most frequently reported drug-related adverse effects were: ocular burning and stinging (10.7%), taste perversion (5.8%), corneal erosion (2.0%), conjunctival injection (1.8%), blurred vision (1.4%), tearing (1.0%), and ocular itching. Urolithiasis was reported rarely (0.9%).

Post-Market Adverse Drug Reactions
The following adverse reactions have been reported in post-marketing experience: dyspnea, respiratory failure, contact dermatitis, bradycardia, heart block, choroidal detachment following filtration surgery, nausea, corneal edema in glaucoma patients with endothelial abnormalities including cellular density and/or morphology, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

DRUG INTERACTIONS

Overview
Specific drug interaction studies have not been performed with dorzolamide and timolol eye drops.

In clinical studies, dorzolamide and timolol eye drops were used concomitantly with the following systemic medications without evidence of adverse interactions: ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs including acetylsalicylic acid, and hormones (e.g., estrogen, insulin, thyroxine). However, the potential for interactions with any drug should be considered.

Drug-Drug Interactions
The following drug interactions have been associated either with the components of VAN-Dorzolamide-Timolol or with other beta-blockers or sulfonamides.

Acid-base Disturbances
The dorzolamide component of VAN-Dorzolamide-Timolol is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, dorzolamide hydrochloride ophthalmic solution was not associated with acid-base disturbances. However, these disturbances have been reported with oral carbonic anhydrase inhibitors and have, in some instances, resulted in drug interactions (e.g., toxicity associated with high-dose salicylate therapy). Therefore, the potential for such drug interactions should be considered in patients receiving VAN-Dorzolamide-Timolol.

Calcium Channel Blockers or Catecholamine-depleting Drugs
The potential exists for additive effects and production of hypotension, atrioventricular conduction disturbances, left ventricular failure and/or marked bradycardia when timolol maleate ophthalmic solution is administered together with oral calcium channel blockers, catecholamine-depleting drugs antiarrhythmics, parasympathomimetics, or beta-adrenergic blocking agents.

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.

Clonidine
Oral ß-adrenergic blocking agents may exacerbate the rebound hypertension which can follow

the withdrawal of clonidine. If the two drugs are coadministered, the ß-adrenergic blocking agent should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by ß-blocker therapy, the introduction of ß-adrenergic blocking agents should be delayed for several days after clonidine administration has stopped.

Beta-adrenergic Blockers
Patients who are already receiving a beta-adrenergic blocking agent systemically and who are given VAN-Dorzolamide-Timolol should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta-blockade. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Epinephrine
Although VAN-Dorzolamide-Timolol used alone has little or no effect on pupil size, mydriasis resulting from concomitant use of timolol maleate and epinephrine has been reported occasionally.

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 and serum uric acid and triglycerides, and slight decreases in hemoglobin and hematocrit and HDL-cholesterol occurred, but were not progressive or associated with clinical manifestations.

Drug-Lifestyle Interactions
Effects on the Ability to Drive and Use Machines
There are side effects of VAN-Dorzolamide-Timolol that may affect some patients' ability to drive and use machines (see DRUG INTERACTIONS and ADVERSE REACTIONS).

DOSAGE AND ADMINISTRATION

Do not allow the pipette to touch the eye or areas around the eye.

Recommended Dose and Dosage Adjustment
The dose is one drop of VAN-Dorzolamide-Timolol (dorzolamide and timolol eye drops) ophthalmic solution in the affected eye(s) two times daily.

A comparative clinical trial of 3 months duration has been performed with dorzolamide and timolol eye drops in adult patients. The results have indicated that the efficacy and safety profile of these two formulations appear to be equivalent. No studies were conducted in special populations (pediatric, kidney or liver diseases, etc.). For details please also refer to the CLINICAL TRIALS section.
When substituting VAN-Dorzolamide-Timolol for another ophthalmic antiglaucoma agent(s), discontinue the other agent(s) after proper dosing on one day, and start VAN-Dorzolamide-Timolol on the next day.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

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.

If the patient has difficulty administering their VAN-Dorzolamide-Timolol eye drops, the assistance of a family member or caregiver may be needed.

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. No data are available with regard to human overdosage by accidental or deliberate ingestion of dorzolamide and timolol eye drops.

There have been reports of inadvertent overdosage with timolol maleate ophthalmic solution 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. The most common signs and symptoms to be expected with overdosage of dorzolamide are electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects (see ADVERSE REACTIONS).

Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyze readily.

Specific Therapeutic Measures for the treatment of overdosage with timolol maleate are reproduced below for ease of reference.

Gastric lavage: If ingested.

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

Dorzolamide and timolol eye drops are a combination of dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intraocular pressure by reducing aqueous humor secretion, but does so by a different mechanism of action.

Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a nonselective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. The combined effect of these two agents results in additional intraocular pressure reduction compared to either component administered alone.

Following topical administration, VAN-Dorzolamide-Timolol reduces elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage. VAN-Dorzolamide-Timolol reduces intraocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

Pharmacokinetics

Dorzolamide Hydrochloride

Unlike oral carbonic anhydrase inhibitors, topically-applied dorzolamide hydrochloride exerts its effects at substantially low doses and therefore with less systemic exposure.

When applied topically, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of selective binding to CA-II while extremely low concentrations of free drug in plasma are maintained. The parent drug forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent drug but also inhibits a less active isoenzyme (CA-I). The metabolite also accumulates in RBCs where it binds primarily to CA-I. Dorzolamide binds moderately to plasma proteins (approximately 33%). Dorzolamide is excreted unchanged in the urine; the metabolite is also excreted in urine. After dosing ends, dorzolamide washes out of RBCs in a non-linear manner, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about four months.

To simulate the maximum systemic exposure after long term topical ocular administration, dorzolamide was given orally to eight healthy subjects for up to 20 weeks. The oral dose of 4 mg/day closely approximates the maximum amount of dorzolamide delivered by topical ocular administration of dorzolamide hydrochloride 2% t.i.d. Dorzolamide and metabolite reached steady state by 4 and 13 weeks, respectively, and the following observations were noted:

- In plasma, concentrations of dorzolamide and metabolite were generally below the assay limit of quantitation (15nM) indicating almost no free drug or metabolite;

- In RBCs, dorzolamide concentrations approached the binding capacity of CA-II (20-25 μM) and metabolite concentrations approached 12-15 μM, well below the binding capacity of

CA-I (125-155 μM);

- In RBCs, inhibition of CA-II activity and total carbonic anhydrase activity was below the degree of inhibition anticipated to be necessary for a pharmacological effect on renal function and respiration.

Timolol Maleate
Timolol maleate is a general beta-adrenergic receptor blocking agent that does not have 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.

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. Dorzolamide is eliminated primarily by urinary excretion as unchanged drug. The metabolic pathway utilized by dorzolamide (cytochrome P-450 2C9, 2C19, and 3A4) is different from that utilized by timolol. In vitro studies using human liver microsomes have shown that dorzolamide at concentrations up to 200 μM does not affect the metabolism of timolol.

Therefore, there is little potential for altered systemic exposure to either drug when administered in combination. 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%. 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 concentration (10 to 20 ng/mL) following oral 5 mg dose, it was estimated that timolol was approximately 50% bioavailable systemically following intraocular administration.

STORAGE AND STABILITY

VAN-Dorzolamide-Timolol
Ophthalmic Solution
Store at 15°- 30°C. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING
VAN-Dorzolamide-Timolol is supplied as a sterile, isotonic, buffered, slightly viscous, aqueous

solution. Each milliliter of VAN-Dorzolamide-Timolol contains 20.00 mg dorzolamide (22.3 mg of dorzolamide hydrochloride) and 5.00 mg timolol (6.83 mg of timolol maleate) as the active ingredients.

Non-medicinal ingredients: sodium citrate dihydrate, hydroxyethyl cellulose, sodium hydroxide solution, mannitol, and water for injection. Benzalkonium chloride (0.0075%) is added as preservative.

VAN-Dorzolamide-Timolol (dorzolamide and timolol eye drops) sterile ophthalmic solution is a slightly opalescent, colourless to nearly colourless, slightly viscous solution supplied in translucent, low- density polyethylene ophthalmic dispensers, with a screw cap and dropper.

Tamper evidence is provided on the container label.

Ophthalmic Solution VAN-Dorzolamide-Timolol, is available in 10 mL dispensers (fill volume of 5 mL per 10 mL bottle).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

VAN-Dorzolamide-Timolol contains dorzolamide hydrochloride and timolol maleate

Dorzolamide Hydrochloride

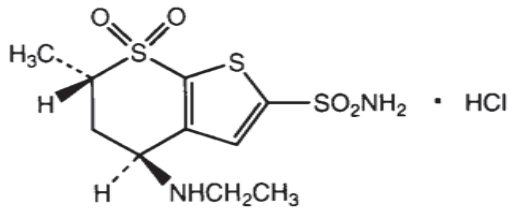
Proper name: dorzolamide hydrochloride

Chemical Name: (4S-*trans*)-4-(Ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide7,7-dioxide monohydrochloride. Dorzolamide hydrochloride is optically active.

Molecular Formula: $C_{10}H_{16}N_2O_4S_3.HCl$

Molecular mass: 360.91

Structural Formula:



Physicochemical Properties

Description: Dorzolamide hydrochloride is a white to off-white, free flowing crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol and has a melting point of about 264°C.

The specific rotation is $\alpha <^{25^\circ}_{405}$ (C=1, water) = ~ -17°.

Timolol Maleate

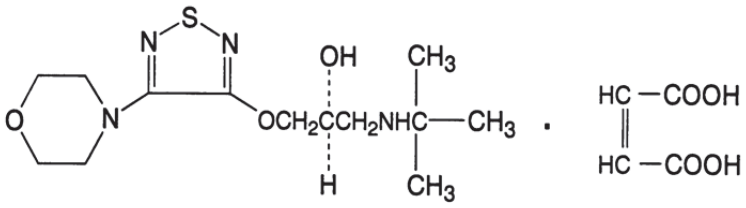
Proper name: timolol maleate

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: $C_{13}H_{24}N_4O_3S.C_4H_4O_4$

Molecular mass: 432.50

Structural formula:



Physicochemical Properties

Description: 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 and has a melting point of 201.5°C to 202.5°C.

CLINICAL TRIALS

Multinational Clinical studies of up to 15 months duration were conducted to compare the IOP-lowering effect of dorzolamide and timolol eye drops b.i.d. (dosed morning and bedtime) to individually- and concomitantly-administered 0.5% timolol and 2.0% dorzolamide in patients with glaucoma or ocular hypertension for whom concomitant therapy is appropriate. This includes both untreated patients and patients inadequately controlled with timolol monotherapy. The IOP-lowering effect of dorzolamide and timolol eye drops b.i.d. was greater than that of monotherapy with either 2% dorzolamide t.i.d. or 0.5% timolol b.i.d. The IOP-lowering effect of dorzolamide and timolol eye drops b.i.d. was equivalent to that of concomitant therapy with dorzolamide b.i.d. and timolol b.i.d.

Comparison to Concomitant Therapy *(Patients initiated on timolol therapy)*

In a 3-month randomized, double-masked, parallel clinical study, patients receiving dorzolamide and timolol eye drops b.i.d. (n = 151) were compared to patients receiving 0.5% timolol b.i.d. plus 2.0% dorzolamide b.i.d. concomitantly (n = 148). At morning trough (hour 0) and morning peak (hour 2), patients receiving dorzolamide and timolol eye drops experienced IOP-lowering that was equivalent to that seen in the patients receiving the individual components concomitantly. The following reductions in IOP were observed relative to the baseline value obtained after 2 weeks of 0.5% timolol b.i.d. monotherapy:

Table I – Additional mean reduction in IOP from timolol baseline (mmHg)[†] [mean % reduction in IOP]

	Day 90 (hour 0)	Day 90 (hour 2)
dorzolamide and timolol eye drops b.i.d.	4.2 [16.3%]	5.4 [21.6%]
0.5% timolol b.i.d. + 2.0% dorzolamide b.i.d.	4.2 [16.3%]	5.4 [21.8%]

[†] Patients were required to have baseline IOP ≥ 22 mmHg for enrollment.

Comparison to Monotherapy

Four 3-month randomized, double-masked parallel clinical studies were conducted to compare dorzolamide and timolol eye drops b.i.d. to 0.5% timolol b.i.d. monotherapy and 2.0% dorzolamide t.i.d. monotherapy. Two studies (n=685) were conducted in patients with baseline IOP ≥ 24 mmHg after a wash-out of all previous ocular hypotensive therapies. The other two studies (n=500) were conducted in patients with elevated IOP ≥ 22 mmHg inadequately controlled after 3 weeks of 0.5% timolol b.i.d. monotherapy. Based upon post-hoc analyses of the combined wash-out studies data and the combined timolol run-in studies data, the estimated difference between the IOP-lowering effects of dorzolamide and timolol eye drops and dorzolamide was 7.8-8.9% at morning trough (hour 0) and 9.9% at morning peak (hour 2), while the estimated difference between the IOP-lowering effects of dorzolamide and timolol eye drops and timolol was 2.9-3.5% at morning trough (hour 0) and 6.9-9.0% at morning peak (hour 2). These differences are statistically significant in favor of the combination.

Long-term Studies

Open-label extensions of two studies were conducted for up to 12 months. During this period, the IOP-lowering effect of dorzolamide and timolol eye drops b.i.d. was demonstrated throughout the day and this effect was maintained during long-term administration.

TOXICOLOGY

Acute Toxicity

The oral LD_{50} of dorzolamide hydrochloride is 1320 mg/kg (3960 mg/m^2) in male and female mice and 1927 mg/kg (11,369 mg/m^2) in female rats.

The oral LD_{50} of timolol maleate is 1190 mg/kg (3570 mg/m^2) in female mice and 900 mg/kg (5310 mg/m^2) in female rats.

Chronic Toxicology

Dorzolamide Hydrochloride and Timolol Maleate

No adverse ocular effects were seen in rabbits and dogs treated topically with dorzolamide and timolol eye drops in studies lasting 3 and 6 months, respectively.

No adverse ocular effects were seen in monkeys and rabbits treated topically with 2% dorzolamide hydrochloride and 0.5% timolol maleate ophthalmic solutions administered concomitantly in studies lasting 15 days and 1 month, respectively.

Timolol Maleate

No adverse ocular effects were observed in rabbits and dogs administered timolol maleate ophthalmic solution topically in studies lasting 1 and 2 years, respectively.

Dorzolamide Hydrochloride

In repeated oral dose toxicity studies of dorzolamide hydrochloride in rodents, dogs and monkeys, the following effects were noted:

- An increased incidence of urothelial hyperplasia was noted in rats and mice. This is a class-effect of carbonic anhydrase inhibitors (CAIs) specific to rodents and is secondary to increased urinary sodium, potassium, pH, and crystals.

- Another class effect of CAIs seen only in rodents was renal papillary cytoplasmic granularity associated with potassium depletion in the kidney. No-effect levels for these microscopic changes were not observed. However, these findings are rodent specific and not seen in monkeys at oral doses up to 50 mg/kg/day (625 times the maximum recommended human ophthalmic dose).

- Metabolic acidosis and the related gastric mucous neck cell hyperplasia were seen in dogs and monkeys. In dogs, the gastric change was seen at a dose as low as 0.2 mg/kg/day in a one-month study, but disappeared with continued dosing and was absent at one year at a dose as high as 2 mg/kg/day. In monkeys in a one-month study, the gastric change was seen at a dose of 50 mg/kg/day orally, but no effects were seen at 10 mg/kg/day orally, or when 0.4 mg/kg/day (~5 times the maximum recommended human ophthalmic dose) was applied topically to the eye for 1 year.

- Another high dose phenomenon observed in dogs and monkeys (doses $\geq$ 1.5 mg/kg/day and 50 mg/kg/day, respectively) in short term studies was decreased remodeling of bone, probably as a result of inhibition of carbonic anhydrase in osteoclasts. Longer term studies in dogs showed the change was transient.

- Marginal nonprogressive decreases in some erythroid parameters were seen in dogs and monkeys at dorzolamide plasma levels of 50 ng/mL in dogs and 1660 ng/mL in monkeys. The plasma levels of dorzolamide in humans given the maximum recommended ophthalmic dose are generally ≤ 5 ng/mL.

Carcinogenicity

Dorzolamide Hydrochloride

In a two-year study of dorzolamide hydrochloride administered orally to male and female Sprague-Dawley rats, urinary bladder papillomas were seen in male rats in the highest dosage group of 20 mg/kg/day (250 times the maximum recommended human ophthalmic dose). Papillomas were not seen in rats given oral doses equivalent to approximately twelve times the maximum recommended human ophthalmic dose. No treatment-related tumors were seen in a 21-month study in female and male mice given oral doses up to 75 mg/kg/day (~900 times the maximum recommended human ophthalmic dose).

The increased incidence of urinary bladder papillomas seen in the high-dose male rats is a class-effect of carbonic anhydrase inhibitors in rats and is secondary to increased urinary sodium, potassium, pH and crystals, all changes induced by carbonic anhydrase inhibitors. Rats are particularly prone to developing papillomas in response to foreign bodies, compounds causing crystalluria and sodium salts of diverse compounds that are inert when given as calcium salts.

No changes in bladder urothelium were seen in dogs given oral dorzolamide for one year at 2 mg/kg/day or in monkeys given oral dorzolamide for one month at 50 mg/kg/day (the urothelial changes in the bladder occurred with oral dosing in rats within one month). In addition, monkeys dosed topically to the eye with 0.4 mg/kg/day (~5 times the maximum recommended human ophthalmic dose) for 1 year had no urothelial changes in the bladder.

Timolol Maleate

In a 2-year oral study of timolol maleate in rats there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (300∗ times the maximum recommended human oral dose). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose.

In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinoma in female mice at 500 mg/kg/day (500 times the maximum recommended human dose), but not at 5 or 50 mg/kg/day. In a subsequent study in female mice, in which post- mortem examinations were limited to uterus and lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinoma was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

Mutagenicity

Dorzolamide Hydrochloride

Dorzolamide hydrochloride was devoid of mutagenic potential when evaluated in the following 5 tests: (1) *in vivo* (mouse) in the cytogenetic assay at doses up to 500 mg/kg/day (6250 times the maximum recommended human ophthalmic dose); (2) *in vitro* in the chromosomal aberration assay; (3) in the alkaline elution assay; (4) in the V-79 assay (doses up to 10 μM); and (5) in the Ames test, in which the highest concentration of dorzolamide hydrochloride used, 10,000 μg/plate, did not result in a two-fold or greater increase in revertants with tester strains of *S. typhimurium* and *E. coli*.

Timolol Maleate

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/mL). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 mcg/plate, were associated with statistically significant elevations ($p \leq 0.05$) 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 for a positive Ames test.

Reproduction

Dorzolamide Hydrochloride

In reproduction studies of dorzolamide hydrochloride in rats, there were no adverse effects on males or females at doses up to 188 or 94 times, respectively, the maximum recommended human ophthalmic dose.

Timolol Maleate

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

Development

Dorzolamide Hydrochloride

There were no treatment-related fetal malformations in developmental toxicity studies with dorzolamide hydrochloride in rats at oral doses up to 10 mg/kg/day (125 times the maximum recommended human ophthalmic dose). Developmental toxicity studies with dorzolamide hydrochloride in rabbits at oral doses of ≥ 2.5 mg/kg/day (31 times the maximum recommended human ophthalmic dose) revealed malformations of the vertebral bodies. These malformations occurred only at doses that caused metabolic acidosis with resultant decreased body weight gain in dams and decreased fetal weights. These malformations, seen only at maternotoxic doses, appear to be a class-effect related to a combination of electrolyte and acid-base changes: decreased venous HCO3-, decreased venous pH and decreased serum potassium. No treatment-related malformations were seen at 1.0 mg/kg/day (13 times the maximum recommended human ophthalmic dose). Acetazolamide, an oral carbonic anhydrase inhibitor, causes skeletal malformations in rats and rabbits by a similar mechanism.

∗ The maximum recommended oral dose is 60 mg of timolol. One drop of timolol maleate 0.5% ophthalmic solution contains about 1/300 of this dose which is about 0.2 mg.

In a study of dorzolamide hydrochloride in lactating rats, decreases in body weight gain of 5 to 7% in offspring at an oral dose of 7.5 mg/kg/day (94 times the maximum recommended human ophthalmic dose), were seen during lactation. A slight delay in postnatal development (incisor eruption, vaginal canalization and eye openings), secondary to lower fetal body weight, was noted at 7.5 mg/kg/day (94 times the maximum recommended human ophthalmic dose).

Timolol Maleate

Teratogenicity studies with timolol in mice and rabbits at doses up to 50 mg/kg/day (50 times the maximum recommended human oral dose) showed no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (1,000 times the maximum recommended human oral dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 100 times the maximum recommended human oral dose, in this case without apparent maternotoxicity.

BIBLIOGRAPHY

1. Boyle JE, Ghosh K, Gieser DK, Adamsons IA, the Dorzolamide-Timolol Study Group. A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol and dorzolamide. Ophthalmology 1998; 105(10):1945-1951.

2. Burstein NL. Corneal cytoxicity of topically applied drugs, vehicles, and preservatives. Surv Ophthalmol 1980; 25(1):15-30.

3. Chapman JM, Cheeks L, Green K. Interactions of benzalkonium chloride with soft and hard contact lenses. Arch Ophthalmol 1990; 108: 244-46.

4. Clineschmidt CM, Williams RD, Snyder E, Adamsons IA, the Dorzolamide-Timolol Study Group. A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. Ophthalmology 1998; 105(10):1952-1959.

5. Hutzelmann J, Owens S, Shedden A, Adamsons I, Vargas E and the International Clinical Equivalence Study Group. Comparison of the safety and efficacy of the fixed combination of dorzolamide/timolol to the concomitant administration of dorzolamide and timolol: a clinical equivalence study. Br J Ophthalmol 1998; 82:1249-53.

6. Katz IM, Kulaga SF, Gould AL, Miller IM, Clineschmidt CM, Wittreich JM. Long-term tolerability and efficacy of timolol ophthalmic solution. Glaucoma 1987; 9:84-8.

7. Laibovitz R, Strahlman ER, Barber BL, Strohmaier KM. Comparison of quality of life and patient preference of dorzolamide and pilocarpine as adjunctive therapy to timolol in the treatment of glaucoma. J Glaucoma 1995; 4(5):306-13.

8. No author. Dorzolamide offers new therapeutic approach in open-angle glaucoma. Drugs Ther Perspect 1994; 3(8):12.

9. Sanchez-Thorin JC. Clinical efficacy of a topical carbonic anhydrase inhibitor in open-angle glaucoma. Chibret Int J Ophthalmol 1994; 10(2):37-41.

10. Strahlman ER, Vogel R, Tipping R, Clineschmidt CM, the Dorzolamide Additivity Study Group. The use of dorzolamide and pilocarpine as adjunctive therapy to timolol in patients with elevated intraocular pressure. Ophthalmology 1996; 103(8):1283-93.

11. Strahlman E, Tipping R, Vogel R, and the International Dorzolamide Study Group. A double-masked, randomized, one year study comparing dorzolamide (TRUSOPT™), timolol and betaxolol. Arch Ophthalmol 1995; 113:1009-16.

12. Strohmaier K, Snyder E, DuBiner H, Adamsons IA, the Dorzolamide-Timolol Study Group. The efficacy and safety of the dorzolamide-timolol combination versus the concomitant administration of its components. Ophthalmology 1998; 105(10):1936-1944.

13. Wilkerson M, Cyrlin M, Lippa EA, Esposito D, Deasy D, Panebianco D, Fazio R, Yablonski M, Shields MB. Four-week safety and efficacy study of dorzolamide, a novel, active topical carbonic anhydrase inhibitor. Arch Ophthalmol 1993; 111(10):1343-50.

14. Zabel R, Mintsioulis G, MacDonald I, Valberg J, Tuft S. Corneal toxic changes after cataract extraction. Can J Ophthalmol 1989; 24(7):311-16.

15. Zimmerman TJ, Kaufman HE. Timolol a ß-adrenergic blocking agent for the treatment of glaucoma. Arch Ophthalmol 1977; 95:601-4.

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

17. Konowal A, Morrison JC, Brown SVL, Cooke DL, Maguire LJ, Verdier DV, et al. Irreversible corneal decompensation in patients treated with topical dorzolamide. Am J Ophthalmol 1999; 127(4):403-6.

18. Product Monograph, COSOPT (dorzolamide hydrochloride and timolol maleate) ophthalmic solution, as marketed by Merck Canada Inc. Submission Control No. 173032, Date of Revision: May 5, 2014.

PART III: CONSUMER INFORMATION

[Pr]VAN-Dorzolamide-Timolol
Dorzolamide and timolol eye drops
BP
20 mg/ml, 5 mg/ml
(as dorzolamide hydrochloride and timolol maleate)

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

ABOUT THIS MEDICATION

What the medication is used for:
VAN-Dorzolamide-Timolol is the brandname for the medication dorzolamide and timolol eye drops available only on prescription through your doctor. VAN-Dorzolamide-Timolol is a combination of an ophthalmic carbonic anhydrase inhibiting drug and an ophthalmic beta-blocking drug, both of which lower the pressure in the eye in different ways.

Remember - This medicine is prescribed for the particular condition that you have.

Do not give this medicine to other people, nor use it for any other condition.

When it should not be used:
Do not use this medicine after the date shown on the container.

Do not use VAN-Dorzolamide-Timolol if you:
- are allergic to any of its components. See "What the important nonmedicinal ingredients are.";
- 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);
- have severe kidney problems;
- are taking oral carbonic anhydrase inhibitors;
- are breast feeding or intend to breast feed.

What the medicinal ingredient is:
Each mL contains 20 mg dorzolamide (as dorzolamide hydrochloride) and 5 mg of timolol (as timolol maleate).

What the important nonmedicinal ingredients are: Hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, sodium hydroxide solution, and water for injection. Benzalkonium chloride is only added as a preservative to VAN-Dorzolamide-Timolol Ophthalmic Solution.

What dosage forms it comes in:
VAN-Dorzolamide-Timolol (dorzolamide and timolol eye drops) are sterile eye drops.

WARNINGS AND PRECAUTIONS

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

- If you have any medical problems now or have had any in the past, lung or breathing (such as asthma or chronic obstructive lung disease) problems or heart problems (such as coronary heart disease, heart failure or low blood pressure);
- If you have any allergies to any medications;
- VAN-Dorzolamide-Timolol Ophthalmic Solution contains the preservative benzalkonium chloride. If you wear contact lenses, you should consult your doctor before using VAN-Dorzolamide-Timolol. Do not administer while wearing (soft) contact lenses. Remove lenses before application and reinsert no earlier than 15 minutes after use.
- If you are pregnant or intend to become pregnant;
- If you are breast feeding or intend to breast feed;
- If you have now or have had in the past kidney problems.
- If you have now or have had in the past liver or thyroid problems.
- If you have now or have had in the past heart rate disturbances (such as slow or irregular heartbeats).
- If you have now or have had in the past poor blood circulation problems (such as Raynaud's syndrome).
- If you have now or have had in the past diabetes or other blood sugar problems.
- If you have certain eye problems (i.e. corneal defects) or history of eye surgery.
- If you are planning major surgery, including eye surgery, as VAN-Dorzolamide-Timolol may change the effects of some medicines during anesthesia.
- If you are taking any other medications see INTERACTIONS WITH THIS MEDICATION.

If the following occur during treatment, consult your doctor immediately:
- allergic reaction such as skin rash or itching.
- develop any eye infection, swelling of the eyelid, redness or irritation.
- you have any eye surgery or suffer eye injury.
- severe skin reactions with symptoms such as blisters, peeling skin, red/purple rash, skin lesions and sores, and associated fever, sore throat

VAN-Dorzolamide-Timolol IS NOT RECOMMENDED FOR

CHILDREN. In studies with dorzolamide and timolol eye drops, the effect of dorzolamide and timolol eye drops was similar in both elderly and younger adult patients.

INTERACTIONS WITH THIS MEDICATION

Your doctor 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 (i.e. calcium channel blockers, clonidine), or to treat heart disease (i.e. quinidine, beta-blockers), diabetes, or depression (i.e. selective serotonin reuptake inhibitors, SSRI's). Also tell your doctor if you are taking large doses of acetylsalicylic acid or sulfa drugs.

PROPER USE OF THIS MEDICATION

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

- Do not start taking any other medicines unless you have discussed the matter with your doctor.
- If you are using VAN-Dorzolamide-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 doctor. If you must stop treatment, contact your doctor 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.

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

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

Missed Dose:
It is important to apply VAN-Dorzolamide-Timolol as prescribed by your doctor. 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.

Overdose:

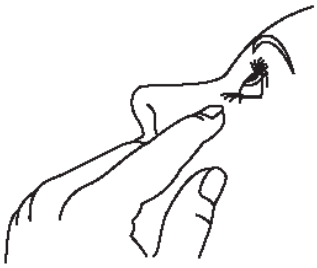
In case of drug overdose, particularly oral ingestion, contact your health care professional, hospital emergency department or regional poison control centre, even if there are no symptoms.

If you feel you have taken too much VAN-Dorzolamide-Timolol and symptoms may include shortness of breath, low heartbeat, dizziness, headache, etc, seek medical help.

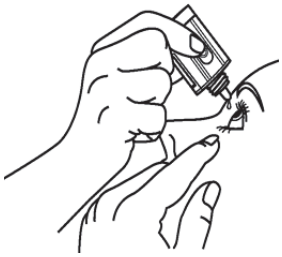
INSTRUCTIONS FOR USE

VAN-Dorzolamide-Timolol Ophthalmic Solution

1. Before using the medication for the first time, be sure the safety seal on the bottle is unbroken.
2. Tear off the safety seal to break the seal.
3. To open the bottle, unscrew the cap by turning. Do not pull the cap directly up and away from the bottle. Pulling the cap directly up will prevent your dispenser from operating properly.
4. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.



5. Invert the bottle and press lightly with the thumb or index (as shown) until a single drop is dispensed into the eye as directed by your doctor.



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 doctor immediately concerning continued use of this bottle.

6. After using VAN-Dorzolamide-Timolol, press a finger into the corner of your eye, by the nose (as shown) for 2 minutes. This helps keep VAN-Dorzolamide-Timolol in your eye.

7. If drop dispensing is difficult after opening for the first time, replace the cap on the bottle and tighten (DO NOT OVERTIGHTEN) and then remove by turning the cap in the opposite direction.

8. Repeat steps 4 & 5 with the other eye if instructed to do so by your doctor.

9. Replace the cap by turning until it is firmly touching the bottle. Do not overtighten or you may damage the bottle and cap.

10. The dispenser tip is designed to provide a single drop; therefore, do NOT enlarge the hole of the dispenser tip.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- Any medicine may have unintended or undesirable effects, so-called side effects.
- You may experience eye symptoms such as burning and stinging, blurred vision, itching, tearing, redness of the eye(s). You may sense a bitter taste after putting in your eye drops. Kidney stones and rarely, rash may also occur.
- Also, other side effects that have been observed with the separate active ingredients in VAN-Dorzolamide-Timolol include: muscle pain, abdominal pain, headache, nosebleed, dry mouth, nausea, tiredness, swelling or crusting of the eyelids.

Other side effects may also occur rarely, and some of these may be serious. These may include shortness of breath, severe skin reactions, visual changes, an irregular heartbeat and a slowing of your heart rate. If you develop a severe skin reaction with symptoms such as blisters, peeling skin, red/purple rash, skin lesions and sores, and associated fever, sore throat, stop taking this medication immediately and contact your physician.

- Your doctor or pharmacist has a complete list of the possible side effects from this medication. Please tell your doctor or pharmacist promptly about any unusual symptom.
- If you have blurred vision or tiredness, do not drive until the effects pass.
- If the contents of the container are swallowed, you should contact your doctor immediately.

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 call your doctor 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 VAN-Dorzolamide-Timolol*, contact your physician or pharmacist.*

HOW TO STORE IT

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

KEEP ALL MEDICINES OUT OF THE 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:

- Call toll-free at 1-866-234-2345
- Report online at www.healthcanada.gc.ca/medeffect
- Complete a Canada Vigilance Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario 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 the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program or Vanc Pharmaceuticals Inc. does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting at:

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Vanc Pharmaceuticals Inc.
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