PRODUCT INFORMATION

STERILE Ophthalmic Solution
0.25% and 0.5%

Trademark
TIMOPTOL®
timolol maleate)

DESCRIPTION

Timolol maleate is a beta-adrenergic receptor blocking agent. Its chemical name is (S)-1-((1,1-dimethyllethyl)amino)-3-((4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl)oxy)-2-propanol, (Z)-butenedioate(1:1)salt. Timolol maleate possesses an asymmetric carbon atom in its structure and is provided as the levo isomer. It has the following structural formula:

![Chemical Structure of Timolol Maleate]

PHARMACOLOGY

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol maleate combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biological 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 biological response.

Ophthalmic Solution TIMOPTOL (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 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 TIMOPTOL is usually rapid, occurring approximately 20 minutes after topical application to the eye. Maximum reduction of intra-ocular pressure occurs in one to two hours. Significant lowering of intraocular pressure has been maintained for as long as 24 hours with 0.25 percent or 0.5 percent TIMOPTOL Ophthalmic Solution. This extended duration of action permits control of intraocular pressure over the usual sleeping hours. Repeated observations over a period of one year indicate that the intraocular pressure lowering effect of TIMOPTOL is well maintained.

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The precise mechanism of action of TIMOPTOL 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, TIMOPTOL 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 TIMOPTOL, a refraction might be necessary when these effects of the miotic have passed.

**CLINICAL STUDIES**

In controlled multiclinic studies in patients with untreated intraocular pressures of 22 mmHg or greater, TIMOPTOL 0.25 percent or 0.5 percent administered twice a day produced a greater reduction in intraocular pressure than 1, 2, 3 or 4 percent pilocarpine solution administered four times a day or 0.5, 1 or 2 percent adrenaline hydrochloride solution administered twice a day.

In the multiclinic studies comparing TIMOPTOL with pilocarpine, 61 percent of patients treated with TIMOPTOL had intraocular pressure reduced to less than 22 mmHg compared to 32 percent of patients treated with pilocarpine.

For patients completing these studies, the mean reduction in pressure at the end of the study from pretreatment was 30.7 percent for patients treated with TIMOPTOL and 21.7 percent for patients treated with pilocarpine.

In the multiclinic studies comparing TIMOPTOL with adrenaline, 69 percent of patients treated with TIMOPTOL had intraocular pressure reduced to less than 22 mmHg compared to 42 percent of patients treated with adrenaline. For patients completing these studies, the mean reduction in pressure at the end of the study from pretreatment was 33.2 percent for patients treated with TIMOPTOL and 28.1 percent for patients treated with adrenaline.

In clinical studies TIMOPTOL produced fewer and less severe side effects than either pilocarpine or adrenaline.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTOL after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least 3 years, no significant difference in mean intraocular pressure has been observed after initial stabilisation.

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

**INDICATIONS**

TIMOPTOL Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure.

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

- Patients with ocular hypertension
- Patients with chronic open-angle glaucoma
- Aphakic patients with glaucoma
CONTRAINDICATIONS

TIMOPTOL is contraindicated in patients with:

- Bronchospasm, bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease.
- Sinus bradycardia; second and third degree atrioventricular block; overt cardiac failure; cardiogenic shock.
- Hypersensitivity to TIMOPTOL Ophthalmic Solution or any component of this product.

PRECAUTIONS

As with other topically applied ophthalmic drugs, this drug may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration.

Cardiac failure should be adequately controlled before beginning therapy with TIMOPTOL. In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

Respiratory complications, including exacerbation of asthma and death due to bronchospasm in patients with asthma, and cardiac complications, including rarely death in association with cardiac failure, have been reported following administration of TIMOPTOL.

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

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOPTOL has little or no effect on the pupil. When TIMOPTOL is used to reduce elevated intraocular pressure in angle-closure glaucoma it should be used with a miotic and not alone.

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

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

Patients should be advised that if they develop an intercurrent ocular condition (e.g. trauma, ocular surgery or infection) or any ocular reactions, particularly conjunctivitis and lid reactions they should immediately seek their physician's advice concerning the continued use of the product.

Ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Risk from Anaphylactic Reaction

While taking β-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. Such patients may be unresponsive to the usual doses of epinephrine use to treat anaphylactic reactions.
Drug Interactions

Although TIMOPTOL used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTOL and adrenaline has been reported occasionally.

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

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope or postural hypotension.

Oral calcium antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function.

The potential exists for hypotension, AV conduction disturbances and left ventricular failure to occur in patients receiving a beta-blocking agent when an oral calcium entry blocker is added to the treatment regimen. The nature of any cardiovascular adverse effect tends to depend on the type of calcium blocker used. Dihydropyridine derivatives, such as nifedipine, may lead to hypotension, whereas verapamil or diltiazem have a greater propensity to lead to AV conduction disturbances or left ventricular failure when used with a beta-blocker.

Intravenous calcium entry blockers should be used with caution in patients receiving beta-adrenergic blocking agents.

The concomitant use of beta-adrenergic blocking agents and digitalis with either diltiazem or verapamil may have additive effects in prolonging AV conduction time.

β adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. Caution should be exercised in patients using these drugs concomitantly. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Use in Pregnancy (Category C)

Beta-adrenergic blocking agents may cause bradycardia in the fetus and newborn infant. During the final part of pregnancy and parturition these drugs should therefore only be given after weighing the needs of the mother against the risk to the fetus.

TIMOPTOL has not been studied in human pregnancy. The use of TIMOPTOL requires that the anticipated benefit be weighed against possible hazards.

Use During Lactation

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.

Use in Children

Safety and effectiveness in children have not been established by adequate and well controlled studies.
SIDE EFFECTS

Ophthalmic solution TIMOPTOL is usually well tolerated. The following adverse reactions have been reported either in clinical trials or since the drug has been marketed.

**Special Senses**

Signs and symptoms of ocular irritation, including burning and stinging, conjunctivitis, blepharitis, keratitis, blepharoptosis, and decreased corneal sensitivity and dry eyes. Visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis, and choroidal detachment following filtration surgery (see PRECAUTIONS), tinnitus.

**Cardiovascular**

Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischaemia, congestive heart failure, palpitation, cardiac arrest, oedema, claudication, Raynaud's phenomenon, cold hands and feet.

**Respiratory**

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), exacerbation of asthma, respiratory failure, dyspnoea, cough.

**Body as a Whole**

Headache, asthenia, fatigue, chest pain.

**Integumentary**

Alopecia, psoriasiform rash or exacerbation of psoriasis.

**Hypersensitivity**

Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash.

**Nervous System/Psychiatric**

Dizziness, depression, insomnia, nightmares, memory loss, increase in signs and symptoms of myasthenia gravis, paraesthesia.

**Digestive**

Nausea, diarrhoea, dyspepsia, dry mouth.

**Urogenital**

Decreased libido, Peyronie's disease.

**Immunologic**

Systemic lupus erythematosus have been reported.
Potential Side Effects

The following side effects have been reported in clinical experience with oral timolol maleate and may be considered potential side effects of ophthalmic timolol maleate.

**Body as a Whole**
- extremity pain
- decreased exercise tolerance

**Cardiovascular**
- AV block (2nd or 3rd degree)
- sinoatrial block
- pulmonary oedema
- worsening of arterial insufficiency
- worsening of angina pectoris
- vasodilation

**Digestive**
- vomiting

**Endocrine**
- hyperglycaemia
- hypoglycaemia

**Integumentary**
- pruritus
- sweating
- exfoliative dermatitis

**Musculoskeletal**
- arthralgia

**Nervous System**
- vertigo
- local weakness

**Psychiatric**
- diminished concentration
- increased dreaming

**Haematologic**
- nonthrombocytopenic purpura

**Respiratory**
- rales

**Urogenital**
- impotence
- micturition difficulties

**Clinical Laboratory Test Findings**

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 haemoglobin, haematocrit, and HDL-cholesterol occurred, but were not progressive or associated with clinical manifestations.
Causal Relationship Unknown

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

**DOSAGE AND ADMINISTRATION**

Recommended therapy is one drop of 0.25 percent solution in the affected eye twice a day.

If clinical response is not adequate, dosage may be changed to one drop of 0.5 percent solution in each affected eye twice a day. If needed, concomitant therapy with miotics, adrenaline and systemically administered carbonic anhydrase inhibitors may be instituted. The use of two topical beta-adrenergic blocking agents is not recommended (see PRECAUTIONS).

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

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.

Systemic absorption of drugs from ophthalmic solutions may be minimised by pressure on the tear-duct immediately after application.

When patients are being transferred from other antiglaucoma agents, monitoring of intraocular pressure is recommended. When a patient is transferred from a single antiglaucoma agent, on the first day continue with the agent already being used and add one drop of 0.25 percent TIMOPTOL in each affected eye twice a day. On the following day, discontinue the previously used antiglaucoma agent completely and continue with TIMOPTOL. If a higher dosage of TIMOPTOL is required substitute one drop of 0.5 percent solution in the eye twice a day. When a patient is transferred from several concomitantly administered antiglaucoma agents, individualisation 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 TIMOPTOL to be useful in patients who respond inadequately to the maximum tolerable antiglaucoma drug therapy.

**OVERDOSAGE**

There have been reports of inadvertent overdosage with TIMOPTOL 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 SIDE EFFECTS).

Contact the Poisons Information Centre for advice on management.
PRESENTATION

Au8895 TIMOPTOL Ophthalmic Solution, clear colourless liquid, 0.25% 5mL ocumeter.

Au8896 TIMOPTOL Ophthalmic Solution, clear colourless liquid, 0.5% 5mL ocumeter.

TIMOPTOL is stable at room temperature.

MANUFACTURER/DISTRIBUTOR

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