

PRODUCT INFORMATION

TENOPT® STERILE Ophthalmic Solution

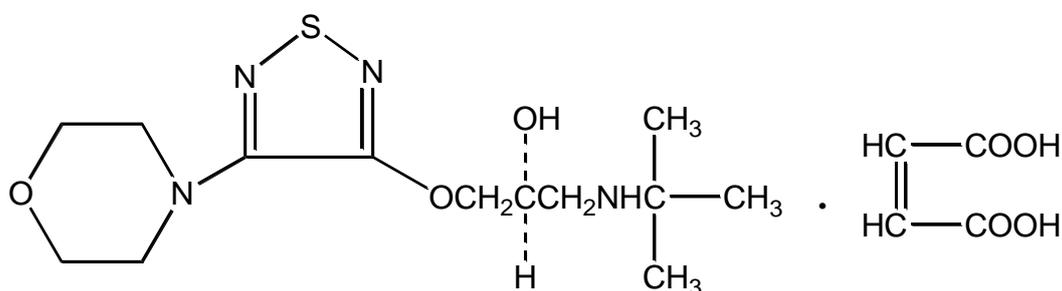
NAME OF THE MEDICINE

TENOPT® (timolol maleate)
0.25% and 0.5%

CAS Number
26921-17-5

Chemical Structure

Timolol maleate is described chemically as (S)-1-((1,1-dimethylethyl)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. The empirical formula is $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ and the structural formula is:



DESCRIPTION

Timolol maleate has a molecular weight of 432.50. It is a white, odourless, crystalline powder which is soluble in water, methanol and alcohol. TENOPT is stable at room temperature.

TENOPT is a clear, colourless to light yellow solution.

Each mL of TENOPT 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of TENOPT 0.5% contains 5.0 mg of timolol (6.8 mg of timolol maleate).

TENOPT also contains the following inactive ingredients: monobasic sodium phosphate dihydrate, dibasic sodium phosphate dodecahydrate, sodium hydroxide and water for injections. Benzalkonium chloride 0.01% is added as preservative.

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 TENOPT (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 TENOPT 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 TENOPT 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 TENOPT is well maintained.

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

Pharmacokinetics

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 less than the lower limit of quantification of the assay, 0.375 ng/mL.

CLINICAL STUDIES

In controlled multiclinic studies in patients with untreated intraocular pressures of 22 mmHg or greater, TENOPT 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 TENOPT with pilocarpine, 61 percent of patients treated with TENOPT 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 TENOPT and 21.7 percent for patients treated with pilocarpine.

In the multiclinic studies comparing TENOPT with adrenaline, 69 percent of patients treated with TENOPT 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 TENOPT and 28.1 percent for patients treated with adrenaline.

In clinical studies TENOPT produced fewer and less severe adverse effects than either pilocarpine or adrenaline.

As with the use of other antiglaucoma drugs, diminished responsiveness to TENOPT 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.

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

INDICATIONS

TENOPT 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

TENOPT is contraindicated in patients with:

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

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

Hypersensitivity to TENOPT 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.

Cardio-respiratory Reactions

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, TENOPT should be discontinued.

Cardiac failure should be adequately controlled before beginning therapy with TENOPT. 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 be given with caution to patients with first degree heart block.

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 TENOPT, alternative therapy should be considered.

Muscle Weakness

Beta-adrenergic blockage has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalised weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.

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 TENOPT.

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

Vascular Disorders

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

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.

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 adrenergic agonists (see ADDITIONAL OVERDOSAGE INFORMATION).

Effects on fertility

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 100 mg/kg/day.

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.

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

Use in 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.

Paediatric use

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

Carcinogenicity

In a 2-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day. Similar differences were not observed in rats administered oral doses of 100 mg/kg/day.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, but not at 50 mg/kg/day. In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumours was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg, but not at doses of 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumours has been established in humans. 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.

Genotoxicity

In vitro and *in vivo* studies (Ames test, neoplastic cell transformation assay, cytogenetic assay and micronucleus test in mice) showed no genotoxicity of timolol.

Other

Patients who are already receiving a beta-adrenergic blocking agent orally and who are given TENOPT 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. TENOPT has little or no effect on the pupil. When TENOPT 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 (eg, timolol, acetazolamide) after filtration procedures.

TENOPT contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses; therefore, TENOPT 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.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. 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.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or disruption of the ocular epithelial surface.

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.

INTERACTIONS WITH OTHER MEDICINES

Although TENOPT used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TENOPT and adrenaline (epinephrine) 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.

The potential exists for additive effects and production of hypotension and/or marked bradycardia when TENOPT is administered together with an oral calcium entry blockers, catecholamine-depleting drugs, antiarrhythmics, parasympathomimetics or beta-adrenergic blocking agents.

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.

Beta-adrenergic blocking agents may exacerbate the rebound hypertension that 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.

ADVERSE EFFECTS

Ophthalmic solution TENOPT is usually well tolerated. 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.

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, 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, abdominal pain

Urogenital

Decreased libido, Peyronie's disease, sexual dysfunction

Immunologic

Systemic lupus erythematosus have been reported.

Musculoskeletal

Myalgia

Potential Adverse Effects

The following adverse effects have been reported in clinical experience with oral timolol maleate and may be considered potential adverse 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 TENOPT 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 (epinephrine) 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 TENOPT may require a few weeks to stabilise, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with TENOPT.

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. This may result in increased local activity.

How to transfer patients from other therapy

When patients are being transferred from other antiglaucoma agents, monitoring of intraocular pressure is recommended.

When a patient is transferred from another topical ophthalmic β -adrenergic blocking agent, that agent should be discontinued after proper dosing on one day and treatment with TENOPT started on the following day with one drop of 0.25% TENOPT in the affected eye twice a day. The dose may be increased to one drop of 0.5% TENOPT twice a day if the clinical response is not adequate.

When a patient is transferred from a single antiglaucoma agent, other than a topical ophthalmic beta-adrenergic blocking agent, on the first day continue with the agent already being used and add one drop of 0.25 percent TENOPT in each affected eye twice a day. On the following day, discontinue the previously used antiglaucoma agent completely and continue with TENOPT. If a higher dosage of TENOPT is required substitute one drop of 0.5 percent solution in each affected 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 TENOPT to be useful in patients who respond inadequately to the maximum tolerable antiglaucoma drug therapy.

OVERDOSAGE

There have been reports of inadvertent overdosage with TENOPT 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 EFFECTS).

Contact the Poisons Information Centre on 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

TENOPT Ophthalmic Solution, clear colourless liquid, 0.25% 5 mL dispensing bottle.
TENOPT Ophthalmic Solution, clear colourless liquid, 0.5% 5 mL dispensing bottle.

All strengths may not currently be marketed in Australia.

Storage conditions

Store below 30°C. Protect from light.
TENOPT is stable at room temperature.

NAME AND ADDRESS OF THE SPONSOR

Mundipharma Pty Limited
ABN 87 081 322 509
88 Phillip Street
Sydney NSW 2000

Further information may be obtained from Mundipharma's Medical Information Department
1800 188 009

POISON SCHEDULE OF THE MEDICINE

S4 Prescription only medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

31 October 1985

DATE OF MOST RECENT AMENDMENT

15 January 2018

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Orbis RA-0138