

Apo-Timop

Timolol maleate 0.25% and 0.5% Ophthalmic solutions USP

Presentation

APO-TIMOP 0.25% is a clear, colourless to light yellow solution containing timolol maleate equivalent to timolol 2.5mg/mL.

APO-TIMOP 0.5% is a clear, colourless to light yellow solution containing timolol maleate equivalent to timolol 5mg/mL.

Uses

Actions

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.

The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established, although a fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However in some studies a slight increase in outflow facility was also observed.

Unlike miotics, APO-TIMOP 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 patients with cataracts the inability to see around lenticular opacities when the pupil constricted by miotics is avoided. When changing patients from miotics to APO-TIMOP a refraction might be necessary when these effects of the miotics have passed.

APO-TIMOP 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.

Pharmacokinetics

Timolol maleate (S(-) enantiomer) is significantly metabolised after oral and ophthalmic administration. Timolol maleate 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 P450 2D6. Timolol is moderately (<60%) bound to plasma proteins.

In a study of plasma drug concentration in 6 subjects, the systemic exposure to timolol was determined following twice daily topical administration to the eye of the 0.5% solution for 8 days. The mean peak plasma concentration following morning dosing was 0.46ng/mL and following afternoon dosing 0.35ng/mL. By comparison to plasma concentrations following oral 5mg dose it was estimated that timolol was approximately 50% bioavailable systemically following intraocular administration.

Onset of action of APO-TIMOP is usually rapid, occurring approximately 20 minutes after topical application to the eye. Maximum reduction of intraocular pressure occurs in one to two hours. Significant lowering of intraocular pressure has been maintained for as long as 24

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hours with 0.25% or 0.5% timolol. This extended duration of action permits control of intraocular pressure over the usual sleeping hours. Repeated observations over a period of three years indicate that the intraocular pressure-lowering effect of timolol maleate is well maintained.

Indications

APO-TIMOP is indicated for the reduction of elevated intraocular pressure. In clinical trials timolol maleate has been shown to reduce intraocular pressure in:

- Patients with ocular hypertension
- Patients with chronic open-angle glaucoma
- Aphakic patients with glaucoma
- Some patients with secondary glaucoma
- Patients with narrow angles and a history of spontaneous or iatrogenically induced narrow-angle closure in the opposite eye in whom reduction of intraocular pressure is necessary

APO-TIMOP is also indicated as concomitant therapy in patients with paediatric glaucoma who are inadequately controlled with other antiglaucoma therapy

Dosage and Administrations

The usual starting dose is one drop of 0.25% APO-TIMOP in the affected eye(s) twice a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5% solution in the affected eye(s) twice a day.

If needed, concomitant therapy with other agents for lowering intraocular pressure may be given with APO-TIMOP. The use of two beta-adrenergic blocking agents is not recommended.

Since in some patients the pressure-lowering response to APO-TIMOP may require a few weeks to stabilise, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment. If the intraocular pressure is maintained at satisfactory levels, many patients can be placed on once-a-day therapy. Because of the naturally occurring diurnal variations in intraocular pressure, satisfactory response is best determined by measuring the intraocular pressure at different times during the day.

How to transfer patients from other therapy:

When a patient is transferred from another topical ophthalmic beta-adrenergic blocking agent, that agent should be discontinued after proper dosing on one day and treatment with APO-TIMOP starting on the following day with one drop of 0.25% APO-TIMOP in the affected eye(s) twice a day. The dose may be increased to 1 drop of 0.5% APO-TIMOP 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, continue the agent already being used and add 1 drop of 0.25% APO-TIMOP in the affected eye(s) twice a day. On the following day, discontinue the previously used antiglaucoma agent completely and continue with APO-TIMOP. If the higher dosage of APO-TIMOP is required, substitute one drop of 0.5% solution in the affected eye(s) twice a day.

Use in children:

The usual starting dose is one drop of 0.25% APO-TIMOP in the affected eye(s) every 12 hours, in addition to other antiglaucoma medication. The dosage may be increased to one drop of 0.5% solution in the affected eye(s) every 12 hours, if necessary. The use of APO-TIMOP is not recommended in premature infants or neonates.

Contraindications

APO-TIMOP is contraindicated in patients with:

- bronchial asthma or other obstructive lung disorders or a history of bronchospasm
- chronic obstructive pulmonary disease
- uncontrolled heart failure (see PRECAUTIONS)
- cardiogenic shock
- sick sinus syndrome
- grade 2 and 3 atrioventricular block and infranodal AV block
- severe bradycardia
- hypersensitivity to any component of APO-TIMOP

Warnings and Precautions

Patients should be warned to avoid allowing the tip of the dropper bottle to contact the eyes or surrounding structures. Patients should be instructed that ocular solutions can become contaminated by bacteria which can cause ocular infections which may result in serious damage to the eye or loss of vision.

Patients should be advised that if they develop an intercurrent ocular condition e.g. trauma, ocular surgery or infection they should seek advice before continuing to use the current multidose container.

There have been reports of bacterial keratitis where containers have been contaminated by patients who have had concurrent corneal disease or a disruption of the ocular epithelial surface.

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

APO-TIMOP is not recommended in patients with conditions susceptible to exacerbation of possible beta-adrenergic blocking effects. It should be used with caution in patients with cardiovascular disease such as sinus bradycardia, first degree block (if the PR interval is greater than 0.24 seconds), second or third degree block and diabetes, especially labile diabetes. Cardiac failure should be adequately controlled before beginning therapy with APO-TIMOP. In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked. 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.

Patients who are already receiving a beta-adrenergic blocking agent orally and who are given APO-TIMOP 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. APO-TIMOP has little or no effect on the pupil. When APO-TIMOP 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.

The preservative in APO-TIMOP may be deposited on soft contact lenses. Soft contact lenses should be removed before administration of the drops and not be reinserted earlier

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than 15 minutes after use. However, APO-TIMOP is generally well-tolerated in patients with glaucoma wearing hard contact lenses.

Risk from anaphylactic reaction:

While taking beta blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Systemic Effects:

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 cause more severe failure.

Continued depression of the myocardium with beta-blocking agents over a period of time can lead to cardiac failure. At the first sign or symptom of cardiac failure use of APO-TIMOP should be discontinued.

The withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of agonists e.g. isoproterenol, dopamine or levarterenol.

Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia and should be used with caution in patients subject to spontaneous hypoglycemia or to diabetic patients receiving insulin or oral hypoglycemic agents.

Beta-adrenergic agents may mask certain clinical signs of hyper thyroidism and patients suspected of developing thyrotoxicosis should be carefully managed to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

Timolol has been reported to increase muscle weakness in some patients with myasthenic symptoms.

Beta-adrenergic blocking agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms indicative of reduced cerebral blood flow develop following initiation of therapy with APO-TIMOP, alternative therapy should be considered.

Use in Pregnancy and Lactation

Category C.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a two 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 300mg/kg/day (300 times the maximum recommended human oral dose). Similar differences were not observed in rats administered oral doses equivalent to 25 to 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 tumours and benign uterine polyps and

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mammary adenocarcinoma in female mice at 500mg/kg/day (500 times the maximum recommended human oral 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 tumours was again observed at 500mg/kg/day.

The increased incidence of mammary adenocarcinoma was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500mg/kg, 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 tumours has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when evaluated in vivo (mouse) in the micronucleus test and cytogenetic assay (doses up to 800mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100mcg/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 TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, 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 and fertility studies in rats showed no adverse effects on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

One drop of APO-TIMOP 0.5% contains about 0.2mg or 1/300 of the maximum recommended human oral dose.

Adverse Effects

APO-TIMOP is usually well tolerated. The following adverse reactions have been reported either in clinical trials or since timolol acetate has been marketed:

Special Senses:

Signs and symptoms of ocular irritations, including burning and stinging, conjunctivitis, blepharitis, keratitis 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 and tinnitus have been reported.

Cardiovascular:

Aggravation or precipitation of certain cardiovascular pulmonary and other disorders presumably related to effects of systemic beta blockade have been reported. Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischemia, 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), respiratory failure, dyspnoea and cough.

Body as a Whole: Headache, asthenia, fatigue, chest pain.

Integumentary:

Alopecia, psoriasiform rash or exacerbation of psoriasis.

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Hypersensitivity:

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

Nervous System/Psychiatric:

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

Digestive:

Nausea, diarrhoea, dyspepsia, dry mouth.

Urogenital:

Decreased libido, Peyronie's disease.

Immunologic:

Systemic lupus erythematosus.

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

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

Interactions

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

The potential exists for additive effects and production of hypotension and/or marked bradycardia when APO-TIMOP is administered together with an oral calcium entry blocker, catecholamine-depleting medicines or beta adrenergic blocking agents.

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting medicines 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 effects 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.



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Potentiated systemic beta-blockade e.g. decreased heart rate has been reported during combined treatment with quinidine and timolol possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme CYP2D6.

Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two medicines are co-administered, the beta-adrenergic blocking agents should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of the beta-adrenergic blocking agent(s) should be delayed for several days after clonidine therapy has stopped.

Overdosage

Systemic effects similar to those seen with systemic beta-adrenergic blocking agents e.g. dizziness, headache, shortness of breath, bradycardia, bronchospasm and cardiac arrest have been reported after inadvertent overdosage with ophthalmic solutions of timolol maleate. The following additional therapeutic measures should be considered:

1. Gastric lavage: If ingested. Studies have shown that timolol does not dialyse readily.
2. Symptomatic bradycardia: Use atropine sulphate intravenously in a dosage of 0.25 to 2mg to induce vagal blockade. If bradycardia persists, intravenous isoprenaline should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.
3. Hypotension: Use sympathomimetic pressor agent therapy, such as dopamine, dobutamine or norepinephrine. In refractory cases the use of glucagon hydrochloride has been reported to be useful.
4. Bronchospasm: Use isoprenaline. Additional therapy with aminophylline may be considered.
5. Acute cardiac failure: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed if necessary by glucagon hydrochloride, which has been reported to be useful.
6. Heart block (second or third degree): Use isoprenaline or a transvenous cardiac pacemaker.

Pharmaceutical Precautions

Protect from heat, light, moisture and contamination.

APO-TIMOP Ophthalmic Solution should be stored at room temperature between 15°C and 25°C.

Once the dropper bottle has been opened, it should be used within one month (30 days).

Medicine Classification

Prescription Only Medicine

Package Quantities

APO-TIMOP 0.25% 5ml dropper bottles, packs of 1.

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Further Information

The product also contains sodium phosphate monobasic monohydrate, sodium phosphate dibasic, benzalkonium chloride and sodium hydroxide.

Name and Address

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