

Timolux

Timolol maleate Ph Eur 0.25% and 0.5% w/v Ophthalmic solutions

Presentation

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

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

Uses

Actions

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

Unlike miotics, timolol maleate reduces intraocular pressure with little or no effect on accommodation or pupil size. Thus, changes in visual acuity due to increased accommodation are uncommon, and dim or blurred vision and night blindness produced by miotics are not evident. In addition, in patients with cataracts the inability to see around lenticular opacities when the pupil is constricted by miotics is avoided. When changing patients from miotics to TIMOLUX a refraction might be necessary when these effects of the miotic have passed.

In clinical studies timolol maleate was generally effective in more patients and produced fewer and less severe adverse effects than either pilocarpine or epinephrine.

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

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

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 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.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

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

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.

Onset of action of timolol maleate 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 hours with 0.25 percent or 0.5 percent timolol maleate. 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.

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

Indications

TIMOLUX 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
- chronic open-angle glaucoma
- Aphakic glaucoma

- Some forms of secondary glaucoma
- narrow angles and a history of spontaneous or iatrogenically induced narrow-angle closure in the opposite eye in whom reduction of intraocular pressure is necessary (see Warnings and Precautions)

TIMOLUX is also indicated as concomitant therapy in patients with paediatric glaucoma, who are inadequately controlled, with other antiglaucoma therapy.

Dosage and Administration

The usual starting dose is one drop of 0.25 percent TIMOLUX 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 percent solution in the affected eye(s) twice a day.

If needed, concomitant therapy with other agent(s) for lowering intraocular pressure may be given with TIMOLUX. The use of two topical beta-adrenergic blocking agents is not recommended (see Warnings and Precautions).

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

If the intraocular pressure is maintained at satisfactory levels, many patients can be placed on once-a-day therapy.

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 TIMOLUX started on the following day with 1 drop of 0.25 percent TIMOLUX in the affected eye twice a day. The dose may be increased to 1 drop of 0.5 percent TIMOLUX 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 percent TIMOLUX in each affected eye twice a day. On the following day, discontinue the previously used antiglaucoma agent completely and continue with TIMOLUX. If a higher dosage of TIMOLUX is required, substitute one drop of 0.5 percent solution in each affected eye twice a day.

Use in Children

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

Contraindications

TIMOLUX is contraindicated in patients with:

- bronchial asthma or other obstructive lung disorders or a history of bronchospasm
- uncontrolled heart failure (see Warnings & Precautions)
- cardiogenic shock
- sick sinus syndrome
- grade 2 and 3 AV block and infranodal AV block
- severe bradycardia
- hypersensitivity to any component of this product

Warnings and Precautions

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

Patients should also be instructed that 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.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g. trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

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 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.

Cardiac failure should be adequately controlled before beginning therapy with TIMOLUX. 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 TIMOLUX.

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

TIMOLUX contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Therefore, TIMOLUX should not be administered while wearing soft contact lenses. The contact lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

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 epinephrine used to treat anaphylactic reactions.

Systemic Effects of Beta-Adrenergic Blocking Agents

Cardiac Failure

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 TIMOLUX should be discontinued.

Major Surgery

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.

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 receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

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.

Muscle Weakness

Beta-adrenergic blockade 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.

General

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 TIMOLUX, alternative therapy should be considered.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product (see Contraindications).

Animal Toxicology

No adverse ocular effects were observed in rabbits and dogs administered with timolol maleate topically in studies lasting one and two years respectively. The oral LD₅₀ of the medicine is 1190 and 900mg/kg in female mice and female rats, respectively.

Carcinogenesis Mutagenesis, Impairment of Fertility

In a two-year oral study of timolol maleate in rats there was a statistically significant ($P < 0.05$) 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 or 100 times the maximum recommended human oral dose.

In a lifetime oral study in mice, there were statistically significant ($P < 0.05$) increases in the incidence of benign and malignant pulmonary tumours and benign uterine polyps and mammary adenocarcinoma in female mice at 500mg/kg/day (500 times the maximum recommended human dose), but not at 5 or 50mg/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 occurrence of mammary adenocarcinoma was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500mg/kg/day, but not at doses of 5 or 50mg/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 man. 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 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 mcg/ml). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 mcg/plate, were associated with statistically significant elevations ($P < 0.05$) 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 effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

* The maximum recommended oral dose is 60mg of timolol. One drop of TIMOLUX 0.5% contains about 1/300 of this dose which is about 0.2mg.

Use in Pregnancy

Category C.

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

Teratogenicity studies with timolol in mice and rabbits at doses up to 50mg/kg/day (50 times the maximum recommended human oral dose) showed no evidence of foetal malformations. Although delayed foetal 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 foetal resorptions. Increased foetal resorptions were also seen in rabbits at doses of 100 times the maximum recommended human oral dose, in this case without apparent maternotoxicity.

Nursing Mothers

Timolol is detectable in human milk. Because of the potential for serious adverse reactions from TIMOLUX 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.

Adverse Effects

Timolol maleate is usually well tolerated. The following adverse reactions have been reported with ocular administration of timolol maleate formulations, either in clinical trials or since the agent 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 (see Warnings and Precautions), tinnitus.

Cardiovascular:

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, 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, paresthesia.

Digestive:

Nausea, diarrhoea, dyspepsia, dry mouth.

Urogenital:

Decreased libido, Peyronie's disease.

Immunologic:

Systemic lupus erythematosus.

Potential Adverse Effects

Adverse effects reported in clinical experience with systemic timolol maleate may be considered potential adverse effects of ophthalmic timolol maleate.

Adverse Effects, Causal Relationship Unknown

The following adverse effects have been reported but a causal relationship to therapy with timolol maleate 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, and retroperitoneal fibrosis, and pseudopemphigoid.

Interactions

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

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.

The potential exists for additive effects and production of hypotension and/or marked bradycardia when TIMOLUX 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 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.

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

β -adrenergic blocking agents should be delayed for several days after clonidine has stopped.

Overdosage

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

The following additional therapeutic measures should be considered:

- Gastric lavage: If ingested. Studies have shown that timolol does not dialyse readily.
- Symptomatic bradycardia: Use atropine sulfate 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.
- 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.
- Bronchospasm: Use isoprenaline. 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 isoprenaline or a transvenous cardiac pacemaker.

Pharmaceutical Precautions

TIMOLUX has an unopened shelf life of 2 years when stored below 25°C.

Once opened TIMOLUX may be stored for a maximum of 4 weeks (28 days) below 25°C.

Medicines Classification

Prescription medicine

Package Quantities

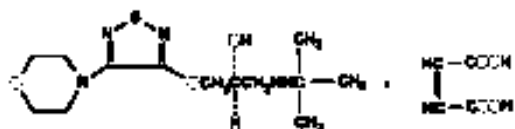
TIMOLUX 0.25% solution 5ml

TIMOLUX 0.5% solution 5ml

Further Information

Chemistry

(Timolol maleate is a β -adrenergic receptor blocking agent.) The chemical name is (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). Timolol maleate possesses an asymmetric carbon atom in the 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:



Timolol maleate has a molecular weight of 432.50. It is a white, odourless, crystalline powder which is soluble in water, methanol, and alcohol. TIMOLUX is stable at room temperature (25°C).

Composition

Each mL of TIMOLUX 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate).
Each mL of TIMOLUX 0.5% contains 5.0 mg of timolol (6.8 mg of timolol maleate).
Inactive ingredients: polyvinyl alcohol, and sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, sodium hydroxide and dilute hydrochloric (to adjust pH), purified water and benzalkonium chloride (preservative).

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