TIMOLENS

Instructions for the medicinal product

Trade name: Timolens.
International Nonproprietary Name: Timolol.
Dosage form: Eye Drops.
Composition: Each ml contains:
Timolol Maleate BP equivalent to Timolol 0.5% w/v;
Benzalkonium chloride Solution BP 0.02% v/v;
(As preservative)
Sterile Aqueous Vehicle q.s.
Pharmacotherapeutic group: Antiglaucoma agents – beta-adrenergic blocker.
ATC Classification: S01ED01.
Pharmacologic property:
Pharmacodynamics:
Timolol is a non-selective β-adrenergic blocker, which does not possess significant intrinsic sympathomimetic or local anaesthetic (membrane-stabilising) activity. When applied topically in the eye, it reduces both elevated and normal intraocular pressure by inhibiting the production of aqueous humour.
Unlike miotics, Timolol reduces intraocular pressure with little or no effect on pupil size or accommodation.
The onset of reduction in intraocular pressure following ocular administration of timolol can be detected within 30 minutes after a single dose The maximum effect usually occurs in one to three hours and significant lowering of intraocular pressure can be maintained for as long as 24 hours following a single dose.
If systemically absorbed, as is possible, Timolol maleate is capable of producing beta-blockade elsewhere in the body with consequent systemic effects (increased airway resistance, bradycardia, hypotension etc.)
Pharmacokinetics:
Following topical instillation in humans, the timolol concentration in aqueous humour was 8-100 ng/ml within the first hour while the mean plasma concentration was approximately 1 ng/ml within the first few hours (compared with plasma concentrations of 5-50 ng/ml seen with therapeutic doses of oral timolol).
Paediatric Population:
As already confirmed by adult data, 80% of each eye drop passes through the nasolacrimal system where it may be rapidly absorbed into the systemic circulation via the nasal mucosa, conjunctiva, nasolacrimal duct, oropharynx and gut, or the skin from tear overflow. Due to the fact that the blood volume in children is smaller than that in adults a higher circulation concentration has to be taken into account. In addition, neonates have immature metabolic enzyme pathways and it may result in an increase in elimination half-life and potentiating adverse events. Limited data show that plasma timolol levels in children after 0.25% greatly exceed those in adults after 0.5%, especially in infants and are presumed to increase the risk of side effects such as bronchospasm and bradycardia.
Indications for use:
Reduction of elevated intraocular pressure in conditions such as:
- Ocular hypertension;
- Chronic open-angle glaucoma (including aphakic patients);
- Some cases of secondary glaucoma.

Contraindications:
- Hypersensitivity to the active substance, any of the excipients or other beta-blocking agents;
- Cardiogenic shock;
- Overt cardiac failure;
- Second and third degree AV block not controlled with pace-maker;
- Sinus bradycardia, sick sinus syndrome sino-atrial block;
- Reactive airway disease including bronchial asthma or a history of bronchial asthma;
- Presence or history of severe chronic obstructive pulmonary disease;
- Severe peripheral circulatory disturbances (Raynaud disease).

Pregnancy and Lactation:
There are no adequate data for the use of timolol in pregnant women. Timolens should not be used during pregnancy unless clearly necessary.
Paediatric Population:
Timolens solutions should generally be used cautiously in young glaucoma patients. It is important to notify the parents of potential side effects so they can immediately discontinue the drug therapy. Signs to look for are for example coughing and wheezing. Because of the possibility of apnoea and Cheyne-Stokes breathing, the drug should be used with extreme caution in neonates, infants and younger children. A portable apnoea monitor may also be helpful for neonates on Timolens.
Dosage and directions for use:
Adults and children over 12 years: recommended therapy is one drop of Timolens 0.5% Eye Drops in the affected eye(s) twice a day.
Elderly:
Dosage need not be modified for the elderly as there has been wide experience with the use of Timolens Eye Drops 0.5% in elderly patients.
When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.
Intraocular pressure should be reassessed approximately four weeks after starting treatment because response to Timolens Eye Drops 0.5% may take a few weeks to stabilise. Provided that intraocular pressure is maintained at satisfactory levels, many patients can then be placed on once daily therapy.
If necessary, concomitant treatment with miotics, epinephrine and/or carbonic anhydrase inhibitors can be instituted. In order to prevent the active substance(s) from being washed out when additional ophthalmic medication is used, an interval of at least 10 minutes between each application is recommended. The use of two topical beta-adrenergic agents is not recommended.
Transfer from other topical beta-blocking agents: Discontinue use after a full day of therapy and start treatment with Timolens Eye Drops 0.5% the next day, with one drop in each affected eye twice daily.
Transfer from a single antiglaucoma agent other than a topical beta-blocking agent:
Continue the agent and add one drop of Timolens Eye Drops 0.5% in each affected eye twice daily. On the following day, discontinue the previous agent completely, and continue with Timolens Eye Drops 0.5%.
Patients should be instructed to remove soft contact lenses before using Timolens.
Paediatric Population:
Due to limited data, Timolens could only be recommended for use in Primary congenital and primary juvenile glaucoma for a transitional period while decision is made on a surgical approach and in case of failed surgery while awaiting further options.
Posology:
Clinicians should strongly evaluate the risks and benefits when considering medical therapy with Timolens in paediatric patients. A detailed paediatric history and examination to determine the presence of systemic abnormalities should precede the use of Timolens.
No specific dosage recommendation can be given as there is only limited clinical data. However, if benefit outweighs the risk, it is recommended to use the lowest active agent concentration available once daily. If IOP could not be sufficiently controlled, a careful up titration to a maximum of two drops daily per affected eye has to be considered. If applied twice daily, an interval of 12 hours should be preferred.
Furthermore the patients, especially neonates, should be strongly observed after the first dose for one to two hours in the office and closely monitored for ocular and systemic side effects until surgery is performed. With regard to paediatric use, the 0.1% active agent concentration might already be sufficient.
Method of administration:
To limit potential adverse effects only one drop should be instilled per dosing time. Systemic absorption of topically administered β-blockers can be reduced by nasolacrimal occlusion and by keeping the eyes closed as long as possible (e.g. for 3 - 5 minutes) after instillation of drops.
Side-effects:
Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.
Immune system disorders: Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylactic reaction.
Metabolism and nutrition disorders: Hypoglycaemia.
Psychiatric disorders: Insomnia, depression, nightmares, memory loss.
Nervous system disorders: Syncope, cerebrovascular accident, cerebral ischemia, increases in signs and symptoms of myasthenia gravis, dizziness, paraesthesia, and headache.
Eye disorders: Signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), blepharitis, keratitis, blurred vision and choroidal detachment following filtration surgery, conjunctivitis, decreased corneal sensitivity, dry eyes, corneal erosion ptosis, diplopia.
Cardiac disorders: Bradycardia, chest pain, palpitations, oedema, arrhythmia, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure.
Vascular disorders: Hypotension, Raynaud's phenomenon, cold hands and feet, intermittent claudication.
Respiratory, thoracic, and mediastinal disorders: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnoea, cough, respiratory failure, nasal congestion.
Gastrointestinal disorders: Dysgeusia, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting.
Skin and subcutaneous tissue disorders: Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.
Musculoskeletal and connective tissue disorders: Myalgia.
Reproductive system and breast disorders: Sexual dysfunction, decreased libido.
General disorders and administration site conditions: Asthenia/fatigue.
Overdose:
No specific data are available. Overdosage is unlikely to occur as one 5ml bottle of Timolens Eye Drops 0.5% contains 25 mgs of Timolens maleate compared with the usual adult oral dose of 20-60 mgs per day. However, in the rare event that overdosage occurs the most common signs and symptoms to be expected following overdosage with a beta-adrenergic receptor blocking agent are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure. If overdosage occurs, the following measures should be considered:
1 Gastric lavage, if ingested. Studies have shown that Timolens cannot be easily removed by hemodialysis.
2 Symptomatic bradycardia: Atropine sulphate, 0.25 to 2mg intravenously, should be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline hydrochloride should be administered cautiously. In refractory cases, the use of a cardiac pacemaker may be considered.
3 Hypotension: A sympathomimetic pressor agent such as dopamine, dobutamine or noradrenaline should be used. In refractory cases, the use of glucagon has been reported to be useful.
4 Bronchopasm: Isoprenaline hydrochloride should be used. 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 which has been reported to be useful.
6 *Heart block (second or third degree):* Isoprenaline hydrochloride or a pacemaker should be used.
Drug interaction:
No specific drug interaction studies have been performed with timolol.
There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympatho-mimetics, guanethidine.
Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.
Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.
Clonidine: increased risk of "rebound hypertension" on discontinuation of clonidine.
Anaesthetic drugs: increased risk of myocardial depression and hypotension due to blockage of cardiac response to reflex sympathetic stimuli.
Cimetidine, hydralazine, phenothiazines and alcohol: may increase plasma level of timolol.
Cautions:
Like other topically applied ophthalmic drugs, Timolens Eye Drops is absorbed systemically. Due to beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.
Cardiac disorders:
In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions. Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.
Vascular disorders
Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.
Respiratory disorders:
Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.
Timolens Eye Drops should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.
Hypoglycaemia/diabetes
Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.
Beta-blockers may also mask the signs of hyperthyroidism.
Corneal diseases
Ophthalmic β-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.
Other beta-blocking agents
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol eye drops is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended.
Anaphylactic reactions
While taking beta-blockers, patients with 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 and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.
Surgical anaesthesia
β-blocking ophthalmological preparations may block systemic β-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.
The lenses should be removed before instillation of the drops and not reinserted earlier than 15 minutes after use.
When Timolol Eye Drops is used to reduce intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.
A reduction in ocular hypotensive response has been reported in some patients following prolonged therapy with Timolol maleate eye drops.
Muscle weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalised weakness). Timolol Eye Drops have been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.
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 any intercurrent ocular condition (e.g. trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of present multi-dose container.
Presentation:
5 ml HDPE Opaque vial in a monocarton, with instruction for use.
Storage:
Keep in dry place protected from light at a temperature below 30°C. Keep out of reach of children.
Shelf life:
Labeled. Do not use after expiry date.
Distribution Condition:
Prescription only medicine (POM).