

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Timolol Eye Drops BP 0.5% w/v

Vistatimol Eye Drops 0.5% w/v

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains: Timolol Maleate BP/Ph Eur equivalent to 5mg/ml timolol

3. PHARMACEUTICAL FORM

Ophthalmic solution

4 CLINICAL PARTICULARS

4.1. Therapeutic Indications

Timolol maleate ophthalmic solution is a beta-adrenergic receptor antagonist used topically for the reduction of elevated intra-ocular pressure in various conditions including patients with ocular hypertension; patients with chronic open-angle glaucoma including patients with aphakia; and some patients with secondary glaucoma.

4.2 Posology and method of administration

Dosage Schedule

Recommended therapy is one drop of Timolol Eye Drops 0.25% w/v in the affected eye(s) twice daily.

If clinical response is not adequate, dosage may be increased to one drop of Timolol Eye Drops 0.5% w/v in the affected eye twice daily. If required, timolol maleate may be used with miotics, adrenaline or systemically administered carbonic anhydrase inhibitors. The use of two topical beta-adrenergic blocking agents is not recommended (See Section 4.4 'Special Warnings and Precautions for Use')

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.

Intra-ocular pressure should be reassessed approximately four weeks after starting treatment because response to Timolol Eye Drops may take a few weeks to stabilise.

Provided that intra-ocular pressure is maintained at satisfactory levels, many patients can then be placed on once-a-day therapy.

Transfer from Other Agents

If transferring from another topical beta-blocking agent, its use should be discontinued after a full day of treatment and treatment with Timolol Eye Drops 0.25% w/v started the next day with one drop twice daily in the affected eye(s). If the clinical response is not adequate, the dosage may be increased to one drop of Timolol Eye Drops 0.5% w/v twice daily.

If transferring from a single anti-glaucoma agent which is not a beta-blocker, the agent should be continued with one drop added of the Timolol Eye Drops 0.25% w/v in the affected eye(s) twice daily. On the following day the previous agent should be discontinued and Timolol Eye Drops continued. The dosage may be increased to Timolol Eye Drops 0.5% w/v twice daily if the clinical response is inadequate.

Paediatric Population

Due to limited data, Timolol 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 Timolol in paediatric patients. A detailed paediatric history and examination to determine the presence of systemic abnormalities should precede the use of Timolol.

No specific dosage recommendation can be given as there is only limited clinical data (see also section 5.1).

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.
See also section 4.4, 5.2.

Duration of treatment:

For a transient treatment in the paediatric population (see also section 4.2 “Paediatric Population”).

Use in the elderly

There has been wide experience with the use of timolol maleate in elderly patients. The dosage recommendations above reflect the clinical data derived from this experience.

4.3. Contraindications

Hypersensitivity to the active substance (substances), or to any of the excipients.

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

Sinus bradycardia, sick sinus syndrome sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.

4.4. Special Warnings and precautions for Use

Like other topically applied ophthalmic agents Timolol Maleate is absorbed systemically. Due to beta-adrenergic component, Timolol Maleate, 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. To reduce the systemic absorption, see 4.2.

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.

Timolol 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 Maleate 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 (see section 4.5).

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 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 Maleate.

If timolol maleate ophthalmic solution is used to reduce elevated intra-ocular pressure in angle closure glaucoma they should be used with a miotic and not alone.

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic receptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy involving beta-blockade should be gradual.

Timolol Eye Drops contain benzalkonium chloride as a preservative, which may be deposited in soft contact lenses. Therefore, timolol eye drops should not be used while wearing soft contact lenses. The lenses should be removed before application of the drops and not reinserted earlier than 15 minutes after use.

Timolol Eye Drops have generally been well tolerated in glaucoma patients wearing conventional hard contact lenses. Timolol maleate ophthalmic solution has not been studied in patients wearing lenses made of material other than polymethylmethacrylate (PMMA) which is used to make hard contact lenses.

Paediatric Population:

Timolol solutions should generally be used cautiously in young glaucoma patients (see also section 5.2).

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 Timolol.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with Timolol Maleate.

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, parasympathomimetics, guanethidine.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

Potentiated systemic betablockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

Oral β -adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

Timolol may potentially add to the effects of oral calcium antagonists, rauwolfia alkaloids or beta-blockers, to induce hypotension and/or marked bradycardia.

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 channel 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.

Those treated with Insulin may find its hypoglycemic activity enhanced.

4.6 Fertility, pregnancy and lactation

Pregnancy There are no adequate data for the use of Timolol Maleate in pregnant women. Timolol Maleate should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see 4.2. Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If Timolol Eye Drops is administered until delivery, the neonate should be carefully monitored during the first days of life.

Lactation Beta-blockers are excreted in breast milk. However, at therapeutic doses of Timolol Maleate in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. *However the decision for breast-feeding mothers either to stop taking timolol eye drops or stop nursing should be based on the importance of the drug to the mother.* To reduce the systemic absorption, see 4.2.

4.7 Effects on ability to drive and use machines

Instillation of Timolol Eye Drops may cause dizziness and transient blurring of vision. Patients should be warned not to drive or operate moving machinery until any dizziness or blurring of vision has totally regressed.

4.8 Undesirable effects

Like other topically applied ophthalmic drugs, Timolol Maleate 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.

Timolol Eye Drops 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. Additional side effects have been reported in clinical experiences with

systemic timolol maleate, and may be considered potential effects of ophthalmic timolol maleate:

Blood and lymphatic system disorders

Non-thrombocytopenic purpura.

Immune system disorders:

Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, systemic lupus erythematosus, pruritus, anaphylactic reaction.

Metabolism and nutrition disorders:

Hypoglycaemia and hyperglycaemia.

Psychiatric disorders:

Insomnia, depression, nightmares, memory loss, increased dreaming, hallucination.

Nervous system disorders:

Syncope, cerebrovascular accident, cerebral ischemia, increases in signs and symptoms of myasthenia gravis, dizziness, diminished concentration, vertigo, paraesthesia, and headache.

Eye disorders:

Signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, and redness), blepharitis, conjunctivitis, keratitis, blurred vision and choroidal detachment following filtration surgery (see 4.4 Special warnings and special precautions for use). Visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases). Decreased corneal sensitivity, dry eyes, corneal erosion ptosis, and diplopia.

Cardiac disorders:

B Bradycardia, chest pain, palpitations, oedema, arrhythmia, congestive heart failure, claudication, sino-atrial block, pulmonary oedema, worsening of arterial insufficiency, worsening of angina pectoris, vasodilation, atrioventricular block, cardiac arrest, cardiac failure.

Vascular disorders:

Ocular: Hypotension, Raynaud's phenomenon, cold hands and feet.

Respiratory, thoracic, and mediastinal disorders:

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnoea, cough, respiratory failure, rales,

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, sweating, exfoliative dermatitis

Musculoskeletal and connective tissue disorders:

Myalgia, arthralgia

Ear and labyrinthine disorders

Tinnitus

Reproductive system and breast disorders:

Sexual dysfunction, decreased libido, Peyronie's disease, impotence, micturition difficulties.

General disorders and administration site conditions:

Asthenia/fatigue, extremity pain, decreased exercise tolerance.

4.9. Overdose

Overdosage reactions are significantly more likely following oral ingestion of timolol maleate than by systemic absorption through topical use. The most common signs and

symptoms to be expected following overdosage with a beta-blocker are dizziness, headache, shortness of breath, bradycardia, bronchospasm and cardiac failure. (See 4.8 'Undesirable effects').

If overdosage does occur the following measures should be considered:

1. Activated charcoal (50g for adults, 1g/kg for children) if the patient presents within 1 hour of taking a significant overdose. Alternatively gastric lavage can be considered for adult patients who present within 1 hour of a potentially life-threatening overdose.
2. Symptomatic bradycardia: atropine sulphate, 0.25 to 2 mg intravenously, should be used to induce vagal blockade. If bradycardia persists, intravenous isoprenaline 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. Bronchospasm: isoprenaline 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 useful.
6. Heart block (second- or third-degree): isoprenaline or a pacemaker should be used.

Studies have shown that timolol does not dialyse readily.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic activity. Timolol maleate combines reversibly with the beta-adrenergic receptor, and this inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the 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.

Unlike miotics, timolol reduces IOP with little or no effect on accommodation or pupil size. In patients with cataracts, the inability to see around lenticular

opacities when the pupil is constricted is avoided. When changing patients from miotics to timolol a refraction might be necessary when the effects of the miotic have passed.

Diminished response after prolonged therapy with timolol has been reported in some patients.

Paediatric Population:

There is only very limited data available on the use of Timolol (0.25%, 0.5% twice daily one drop) in the paediatric population for a treatment period up to 12 weeks. One small, double blinded, randomized, published clinical study conducted on 105 children (n=71 on Timolol) aged 12 days – 5 years show to some extent evidence, that Timolol in the indication *primary congenital and primary juvenile glaucoma* is effective in short term treatment.

5.2 Pharmacokinetic properties

The onset of reduction in intra-ocular pressure can be detected within one-half hour after a single dose. The maximum effect occurs in one or two hours; significant lowering of IOP can be maintained for as long as 24 hours with a single dose.

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.

5.3 Preclinical safety data

No adverse ocular effects were observed in rabbits and dogs administered timolol maleate eye drops topically in studies lasting one and two years, respectively. The oral LD₅₀ of the drug is 1,190 and 900 mg/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 ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/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 ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinoma in female mice at 500 mg/kg/day (500 times the maximum recommended human 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 500 mg/kg/day.

The increased occurrence of mammary adenocarcinoma was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg/day, 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 man. 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.

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, 5,000 or 10,000 mcg/plate, were associated with statistically significant ($p \leq 0.05$) elevations 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium Dihydrogen Phosphate
Disodium Hydrogen Phosphate Dodecahydrate
Benzalkonium Chloride
Purified Water

6.2. Incompatibilities

None known.

6.3. Shelf Life

36 months unopened.
28 days after opening.

6.4 Special precautions for storage

Do not store above 30°C. Store in the outer container.

6.5. Nature and contents of Container

A 5ml low density polyethylene eye dropper bottle. The dropper insert is made from low density polyethylene and the bottle is closed by a tamper evident screw cap manufactured from high density polyethylene. Pack size 1 x 5ml

6.6 Special precautions for disposal and other handling

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.

7 MARKETING AUTHORISATION HOLDER

Martindale Pharmaceuticals Ltd
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RM3 8UG

8 MARKETING AUTHORISATION NUMBER(S)

PL 0156/0033

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

15/01/2021