

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Timoptol 0.5% w/v Eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Timolol Maleate equivalent to 0.5 % w/v solution of timolol (5 mg/ml).

Also includes benzalkonium chloride.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Eye drops, solution

Product imported from Belgium:

Clear, colourless to light yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Timoptol 0.5% w/v Eye Drops Solution is a beta-adrenoreceptor blocking agent used topically in the reduction of elevated intra-ocular pressure in various conditions including the following: patients with ocular hypertension; patients with chronic open-angle glaucoma including aphakic patients; some patients with secondary glaucoma.

4.2 Posology and method of administration

Recommended therapy is one drop 0.25% solution in the affected eye twice a day.

If clinical response is not adequate, dosage may be changed to one drop 0.5% solution in each affected eye twice a day. If needed, Timoptol may be used with other agent(s) for lowering intra-ocular pressure. The use of two topical beta-adrenergic blocking agents is not recommended (see 4.4 'Special warnings and special precautions for use').

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

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

Transfer from other agents

When another topical beta-blocking agent is being used, discontinue its use after a full day of therapy and start treatment with Timoptol the next day with one drop of 0.25% Timoptol in each affected eye twice a day. The dosage may be increased to one drop of 0.5% solution in each affected eye twice a day if the response is not adequate.

When transferring a patient from a single anti-glaucoma agent other than a topical beta-blocking agent, continue the agent and add one drop of 0.25% Timoptol in each affected eye twice a day. On the following day, discontinue the previous agent completely, and continue with Timoptol. If a higher dosage of Timoptol is required, substitute one drop of 0.5% solution in each affected eye twice a day.

Paediatric use

Is not currently recommended.

Use in the elderly

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

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 be informed of the correct handling of the OCUMETER PLUS bottles.

Usage instructions

1. Before using the medication for the first time, be sure the safety strip on the front of the bottle is unbroken. A gap between the bottle and the cap is normal for an unopened bottle.
2. Tear off the safety strip to break the seal.
3. To open the bottle, unscrew the cap by turning as indicated by the arrows.
4. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.
5. Invert the bottle, and press lightly with the thumb or index finger over the "Finger Push Area" until a single drop is dispensed into the eye as directed by your doctor. **DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.**
6. If dispensing is difficult after opening for the first time, replace the cap on the bottle and tighten (DO NOT OVERTIGHTEN) and then remove by turning the cap in the opposite direction as indicated by the arrows on top of the cap.
7. Repeat steps 4 and 5 with the other eye if instructed to do so by your doctor.
8. Replace the cap by turning until it is firmly touching the bottle. The arrow on the cap must line up with the arrow on the bottle for proper closure. Return the bottle to the original outer carton.
9. The dispenser tip is designed to provide a pre-measured drop; therefore, do NOT enlarge the hole of The dispenser tip.
10. After you have used all doses, there will be some 'Timoptol' Ophthalmic Solution left in the bottle.
11. You should not be concerned since an extra amount of solution has been added and you will get the full amount of 'Timoptol' Ophthalmic Solution that your doctor prescribed. Do not attempt to remove the excess medicine from the bottle.

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.

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 is absorbed systemically. Due to betaadrenergic 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. 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.

Timoptol 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.

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be exaggerated when *Timoptol* is given to 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.

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 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.

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoreceptor 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.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

The Ocumeter dispenser of Timoptol contains benzalkonium chloride as a preservative which may be deposited on soft contact lenses; therefore, Timoptol should not be used while wearing these lenses. The lenses should be removed before application of the drops and not reinserted earlier than 15 minutes after use.

Timoptol has been generally well tolerated in glaucoma patients wearing conventional hard contact lenses. Timoptol has not been studied in patients wearing lenses made with material other than polymethylmethacrylate (PMMA), which is used to make hard contact lenses.

In patients with angle-closure glaucoma, the immediate objective of treatment is to re-open the angle. This requires constricting the pupil with a miotic. Timoptol has little or no effect on the pupil. When Timoptol is used to reduce elevated intra-ocular pressure in angle-closure glaucoma it should be used with a miotic and not alone.

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 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.

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.

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.

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 (adrenaline) used to treat anaphylactic reactions.

Benzalkonium chloride may cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with timolol.

Although Timoptol alone has little or no effect on pupil size, mydriasis has occasionally been reported when Timoptol is given with epinephrine (adrenaline).

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.

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.

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

Timoptol 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 entry 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data for the use of timolol in pregnant women. Timolol 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 Timoptol 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 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. To reduce the systemic absorption, see 4.2.

4.7 Effects on ability to drive and use machines

Possible side effects such as dizziness and visual disturbances may affect some patients' ability to drive or operate machinery.

4.8 Undesirable effects

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.

Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with Timptol:

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 (see 4.4 Special warnings and special precautions for use). decreased corneal sensitivity, dry eyes, corneal erosion ptosis, diplopia.

Special senses

Signs and symptoms of ocular irritation, including burning and stinging, conjunctivitis, blepharitis, keratitis, dry eyes, and decreased corneal sensitivity. Tinnitus, visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis and choroidal detachment following filtration surgery (see Section 4.4 'Special warnings and special precautions for use').

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.

Respiratory, thoracic, and mediastinal disorders:

Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnoea, cough.

Body as a whole

Headache, asthenia, fatigue, chest pain.

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.

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.

Urogenital

Decreased libido, Peyronie's disease.

Immunologic

Systemic lupus erythematosus.

General disorders and administration site conditions:

Asthenia/fatigue.

Causal relationship unknown

The following adverse effects have been reported, but a causal relationship to Timoptol 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 psychiatric disturbances), hypertension, retroperitoneal fibrosis and pseudopemphigoid.

The adverse reactions seen with oral timolol maleate may occur with Timoptol.

Potential side effects

The following additional side effects have been reported in clinical experiences with systemic timolol maleate, and may be considered potential effects of ophthalmic timolol maleate:

Body as a whole

Extremity pain, decreased exercise tolerance.

Cardiovascular

AV block (second- or third-degree), sinoatrial block, pulmonary oedema, worsening of arterial insufficiency, worsening of angina pectoris, vasodilatation.

Digestive

Vomiting

Endocrine

Hyperglycaemia, hypoglycaemia.

Integumentary

Pruritus, sweating, exfoliative dermatitis.

Musculoskeletal

Arthralgia.

Nervous system

Vertigo, local weakness.

Psychiatric

Diminished concentration, increased dreaming.

Haematologic

Non-thrombocytopenic purpura.

Respiratory

Rales.

Urogenital

Impotence, micturition difficulties.

4.9 Overdose

There have been reports of inadvertent overdosage with Timoptol 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 Section 4.8 ‘Undesirable effects’).

If overdosage occurs, the following measures should be considered:

1. Gastric lavage, if ingested. Studies have shown that Timolol does not dialyse readily.
2. Symptomatic bradycardia: Atropine sulphate, 0.25 to 2 mg 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. Bronchospasm: 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 useful.
6. Heart block (second- or third-degree): Isoprenaline hydrochloride or a pacemaker should be used.

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, Timoptol 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 Timoptol a refraction might be necessary when the effects of the miotic have passed.

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

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.

5.3 Preclinical safety data

No adverse ocular effects were observed in rabbits and dogs administered Timoptol 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 500mg/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

Benzalkonium chloride as preservative
Disodium phosphate dodecahydrate

Sodium dihydrogen phosphate dihydrate
Sodium hydroxide
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date for this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

The product should be used within 28 days after first opening the container.

6.4 Special precautions for storage

Store below 25°C.

Store bottle in the outer carton in order to protect from light. Ensure the container is properly closed.

6.5 Nature and contents of container

The OCUMETER Plus ophthalmic dispenser consists of a translucent high-density polyethylene container with a sealed dropper tip, a flexible fluted side area, which is depressed to dispense the drops, and a two-piece assembly. The two-piece cap mechanism punctures the sealed dropper tip upon initial use, then locks together to provide a single cap during the usage period. Tamper evidence is provided by a safety strip on the container label. The OCUMETER Plus ophthalmic dispenser contains 5 ml of solution.

Timoptol Ophthalmic Solution is available in single bottles containing 5 ml of solution.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused product should be disposed of in accordance with local requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1562/52/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd June 2011

10 DATE OF REVISION OF THE TEXT

May 2012