1.6 Product Information

1.6.1 Summary of Product characteristics.
AUROTIM (Timolol Eye Drops 0.5%w/v)

1. Name of the medicinal product
AUROTIM

2. Qualitative and quantitative composition
Timolol Maleate BP equivalent to Timolol 0.5%w/v
For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Eye drops, solution.
Clear, colorless aqueous solution, practically free from visible particles.

4. Clinical particulars
4.1 Therapeutic indications
Timolol Eye Drops is a beta-adrenoreceptor blocking agent used topically in the reduction of elevated intra-ocular pressure in various conditions. It is indicated in adult patients with ocular hypertension; adult patients with chronic open-angle glaucoma including aphakic patients; some adult patients with secondary glaucoma.

4.2 Posology and method of administration
Adults:
Posology:
Recommended therapy is one drop of 2.5 mg/ml solution in the affected eye, once or twice (morning and evening) a day.
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.
If clinical response is not adequate, dosage may be changed to one drop of 5 mg/ml solution in each affected eye, once or twice (morning and evening) a day. If needed, Timolol Eye Drops 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).
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 the intra-ocular pressure is maintained at satisfactory levels, many patients can then be placed on once-a-day therapy of Timolol Eye Drops.

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 a 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 medical 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 intra-ocular pressure (IOP) could not be sufficiently controlled, a careful up titration to a maximum of two drops of 5 mg/ml timolol eye drops solution 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 closely 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.

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 sections 4.4, 5.2.

Duration of treatment:
For a transient treatment in the paediatric population.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
As with all products containing beta-receptor blocking agents, Timolol Eye Drops is contraindicated in patients with:
• 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 (AV) 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 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. To reduce the systemic absorption, see section 4.2.

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 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).
In patients with closed-angle glaucoma, Timolol Eye

Drops should be used in combination with miotics, as the immediate purpose of the treatment is to reopen the chamber angle which requires a constriction of the pupil. Timolol has little or no effect on the pupil.

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

Anaphylactic reactions
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, and may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

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 beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Surgical anaesthesia
Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving Timolol.
Timolol Eye Drops should also be used with great care in connection with the following diseases and conditions:
• Myasthenia: Beta-adrenergic blocking may potentiate muscle weakness corresponding to certain myasthenia symptoms (e.g. diplopia, ptosis, general weakening).
• Untreated pheochromocytoma.
• Metabolic acidosis.

• Large surgical procedures: It is recommended to gradually decrease the use of adrenergic beta-blocking drugs prior to the procedure in order to avoid the reflex stimuli of the beta-blockers on the heart and thus lessen the risk of hypertension and cardiac arrest during the anaesthesia.
• Intermittent claudication.
• Severely reduced kidney function. With dialysis patients, pronounced drop in blood pressure has been observed.
Patients with a history of contact hypersensitivity to silver should not use this product as dispensed drops may contain traces of silver.
Timolol Eye Drops has not been studied in patients using contact lenses.
Timolol Eye Drops should not be used while using soft contact lenses. The lenses should only be inserted 15 minutes after the drip.

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 (see section 4.8). 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.
Cases of mydriasis have been reported with simultaneous use of ophthalmological beta-blockers and adrenalin. Even though Timolol administered by itself has little or no effect on the size of the pupil, close ophthalmological monitoring is advised.
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.
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.
Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.
Timolol potentiates the effect of other drugs with effect on the bulbous tension.
Beta-blockers may increase the hypoglycaemic effect of insulin and oral anti-diabetic drugs and mask signs and symptoms of hypoglycaemia (see point 4.4).
If more than one ophthalmic drug is used, at least 5 minutes have to pass between using the different eye drops.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data for the use of Timolol in pregnant women. Timolol Eye Drops 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.

Breast-feeding

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. To reduce the systemic absorption, see 4.2.

Fertility

Non clinical data do not show any effects of Timolol on male or female fertility.

4.7 Effects on ability to drive and use machines

It has minor influence on the ability to drive and use machines. While driving vehicles or operating different machines, it should be taken into account that occasionally visual disturbances may occur including refractive changes, diplopia, ptosis, frequent episodes of mild and transient blurred vision and occasional episodes of dizziness or fatigue.

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.

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:
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.

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
Symptoms of overdosage are similar to those seen with systemic beta adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, cardiac arrest, acute cardiovascular insufficiency and hypotension (see section 4.8).
If overdosage occurs, the following measures should be considered:
1. Administration of activated charcoal, if the preparation has been taken orally. Studies have shown that Timolol maleate cannot be removed by haemodialysis.
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 given. Concomitant 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 recommended. 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

Pharmacotherapeutic group: Ophthalmologicals, antiglaucoma preparations and miotics, betablocking agents, ATC - code: S01ED01

Mechanism of action

Timolol Eye Drops (Timolol-maleate) is a non-selective beta-receptor blocker without beta-stimulating effect or significant membrane stabilizing local anaesthetic effect.

Pharmacodynamic effects

The pressure reducing effect of Timolol-maleate is more likely due to reduced influx of chamber fluid than an increased out flow, however, it is still unclear whether the pressure effect is a pure beta-blocking effect. The drug does not influence blood pressure and heart rate.

Clinical efficacy and safety

Clinical studies show that Timolol eye drops lower the intraocular pressure in glaucomatous eyes. No or insignificant changes in pupil size or visual acuity have been observed.

Paediatric Population:

There is only very limited data available on the use of Timolol (2.5 mg/ml, 5 mg/ml twice daily one drop) in the paediatric population. In one small, double masked, randomized, published clinical study conducted for a treatment period of up to 12 weeks on 105 children (n=71 on Timolol) aged 12 days – 5 years the data have shown 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

Absorption

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.

In some cases, a decreased therapeutic effect has been observed in long-term treatment.

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 2.5 mg/ml greatly exceed those in adults after 5 mg/ml, 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 topically in studies lasting one and twelve months.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. Pharmaceutical particulars

6.1 List of excipients

Disodium hydrogen ortho phosphate BP
Sodium dihydrogen ortho phosphate BP
Benzalkonium chloride BP
Purified Water BP

6.2 Incompatibilities

None known.

6.3 Shelf life

24months unopened.
Discard 28 days after first opening.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

5ml filled in 10ml Low density polyethylene container with HDPE cap and Nozzle. Such 10ml is packed in a monocarton with package insert.

6.6 Special precautions for disposal and other handling

There is no special requirement for disposal.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Aurolab, No.1,
Sivagangai Main road,
Veerapanjan,
Madurai - 625020,
India.

8. Marketing authorisation number(s)

TN00002387

9. Date of first authorisation/renewal of the authorisation

11.07.2022

10. Date of revision of the text

Not Applicable