SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Timolol Maleate 0.5 % ophthalmic solution
Glaucol 0.5 %

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Timolol 0.5 w/v
as Timolol Maleate BP 0.68 w/v

3 PHARMACEUTICAL FORM

Sterile aqueous 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 0.25% solution in the affected eye(s) twice a day.

If clinical response is not adequate, dosage may be increased to one drop 0.5% solution in the affected eye(s) twice daily. If required Timolol Maleate ophthalmic solution may be used with miotics, adrenaline or systemically-administered carbonic anhydrase inhibitors.

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 Maleate eye-drops may take a few weeks to stabilise.

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 Maleate 0.25% eye-drops started the next day with one drop twice daily in the affected eye(s). As above, if the clinical response is not adequate, the dosage may be increased to one drop of the 0.5% solution twice daily.

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

Use in the elderly:

There is a wide difference with the usage of this product in elderly patients. The dosage recommendations above reflect the clinical data derived from this experience.

Use in children:

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

Route of Administration: topical eye-drops.

4.3 Contraindications

- Reactive airway disease including bronchial asthma, history of bronchial asthma, or severe chronic obstructive pulmonary disease
- sinus bradycardia, sick sinus syndrome sino-artial block, second and third degree AV block not controlled with a pace-maker, overt cardiac failure, cardiogenic shock
- hypersensitivity to the active substance (Timolol Maleate), or other beta-blocking agents, or to any of the excipients

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic drugs, Timolol Maleate ophthalmic solution may be absorbed systemically and due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemically administered beta-blockers may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for system 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 closely observed 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 ophthalmic solution 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 exaggerated when Timolol Maleate ophthalmic solution is given to patients already receiving an oral beta-blocking agent. The response of these patients should be closely watched. 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 ophthalmic solution

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.

If Timolol Maleate ophthalmic solution is used to reduce elevated intra-ocular pressure in angle closure glaucoma it 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.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with Timolol ophthalmic solution.

Although Timolol Maleate ophthalmic solution alone has little or no effect on pupil size, mydriasis has occasionally been reported when Timolol Maleate ophthalmic solution is given with adrenaline.

Small amounts of Timolol Maleate ophthalmic solution may be absorbed systemically and potentially interact with other drugs.

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 antagonists, beta-adrenergic blockers, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

Oral calcium-channel blockers increase the risk of bradycardia, hypotension, AV block, asystole and heart failure.

Anti-arrhythmic drugs such as amiodarone and quinidine may potentiate beta-blockade. Cimetidine may increase the plasma concentration of timolol maleate.

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.

4.6 Pregnancy and lactation

Pregnancy:

There are no adequate data for the use of timolol in pregnant women. Timolol ophthalmic solution 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 ophthalmic solution 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

Installation of Timolol Maleate eye-drops may cause transient blurring of vision. Patients should be warned not to drive or operate moving machinery until any blurring of vision after installation has totally regressed.

4.8 Undesirable effects

Timolol Maleate ophthalmic solution is usually well tolerated.

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, localised and generalised 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

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

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

4.9 Overdose

Overdosage reactions are more likely to follow oral ingestion of Timolol Maleate than by systemic absorption through its topical use. No specific data on overdosage in humans by either route are available.

A study in patients with renal failure suggests that Timolol does not readily dialyse.

The most common signs and symptoms to be expected following overdosage with a beta-blocker are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure. The standard measures to overcome beta blockade should under taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Timolol Maleate is a non-selective beta-adrenergic antagonist used as an ophthalmic solution for the topical treatment of increased intra-ocular pressure.

Timolol Maleate has no intrinsic sympathomimetic activity nor membrane-stabilising activity.

It is thought that the mode of action is by markedly reducing the production of aqueous humor, probably without any effect on the outflow tract.

Timolol Maleate ophthalmic solution is effective in a range of concentrations but the usual recommendation is for 0.25% and 0.5% solution strengths.

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

Timolol Maleate ophthalmic solution lowers intra-ocular pressure within 30-60 minutes of being administered topically, has a maximum iop-lowering effect 4-5 hours after administration, and the effect persists for 12-14 hours after a single dose.

Minute amounts are absorbed systemically; plasma concentrations of up to 1 Ng/ml can be detected after single eye-drop administration.

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

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide
Water for injections

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Protect from light.
Store below 25°C.

6.5 Nature and contents of container

Uni-dose vials made from LDPE (Lupolen 1840H) Ph. Eur. grade supplied in 30 vial pack (3 x 10 vials) enclosed in sealed aluminium foil pouch and cartoned.

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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