National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
TIMOLOL 0.25% EYE DROP SMPC

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Timolol Eye Drops 0.25%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Timolol (as Timolol maleate) 5.0mg/ml

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL form

Eye drops, solution.

4. Clinical particulars

4.1 Therapeutic indications

Reduction of elevated intraocular pressure in conditions such as:

- Ocular hypertension;
- Chronic open-angle glaucoma (including aphakic patients);
- Some cases of secondary glaucoma

4.2 Posology and method of administration

Adults and children over 12 years: recommended therapy is one drop of Timolol 0.25% 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 Timolol Eye Drops 0.25% 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 Timolol Eye Drops 0.25% 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 Timolol Eye Drops 0.25% 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 Timolol Eye Drops 0.25% in each affected eye twice daily. On the following day, discontinue the previous agent completely, and continue with Timolol Eye Drops 0.25%.

Patients should be instructed to remove soft contact lenses before using timolol.

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”)”.

4.3 Contraindications

Timolol Eye Drops 0.25% is contraindicated in patients with:

• 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);

• Hypersensitivity to the active substance, any of the excipients or other beta-blocking agents.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic drugs, Timolol 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. 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 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 (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.

This formulation of Timolol Eye Drops contains benzalkonium chloride as a preservative which may be deposited in soft contact lenses. Hence, Timolol Eye Drops should not be used while wearing these lenses. 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.

There have been reports of bacterial keratitis associated with the use of topical ophthalmic products.

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.

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, 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.

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.

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 Timolol Eye Drops is administered until delivery, the neonate should be carefully monitored during the first days of life.Timolol Eye Drops 0.25% has not

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.Timolol

4.7 Effects on ability to drive and use machines

There are currently no data available on the effects of Timolol Eye Drops 0.25% on the ability to drive or use machinery. It has to be taken into account that dizziness, fatigue, transient ocular irritation, blurred vision and lacrimation may occur occasionally.

4.8 Undesirable 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 (see 4.4 Special warnings and special precautions for use), 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.

<u>The following adverse events have been reported but a causal relationship to therapy with timolol eye drops has not been established:-</u>

Metabolism & nutrition disorders: anorexia

Psychiatric disorders: behavioural disorders including confusion, hallucination, anxiety, disorientation, nervousness, somnolence, psychic disturbances.

Eye disorders: aphakic cystoids macular oedema

Cardiac disorders: angina pectoris aggravated

Vascular disorders: hypertension, pulmonary oedema

Gastrointestinal disorders: retroperitoneal fibrosis

Skin and subcutaneous tissue disorders: pemphigoid

Reproductive system and breast disorders: impotence

<u>The following additional adverse events have been reported with oral timolol maleate and may be considered as potential effects of ophthalmic timolol maleate:-</u>

Blood & lymphatic system disorders: purpura non-thrombocytopenic

Metabolism & nutrition disorders: weight loss, hyperglycaemia

Nervous system disorders: vertigo

Psychiatric disorders: concentration impaired

Ear disorders: tinnitus

Vascular disorders: arterial insufficiency, vasodilation

Respiratory, thoracic, and mediastinal disorders: rales, bronchial obstruction,

Hepatobiliary disorders: hepatomegaly

Skin and subcutaneous tissue disorders: skin irritation, pigmentation abnormal, sweating

Musculoskeletal & connective tissue disorders: pain in extremity, arthralgia

Renal and urinary disorders: dysuria

General disorders and administration site conditions: exercise tolerance decreased

In addition, the following additional adverse events have been reported with other beta-adrenergic blocking agents and may be considered as potential effects of ophthalmic timolol maleate:-

Immune system disorders: fever combined with general muscle aches, throat sore, laryngospasm and respiratory distress.

Blood & lymphatic system disorders: agranulocytosis, thrombocytopenic purpura

Psychiatric disorders: catatonia, an acute reversible syndrome (disorientation, memory loss, emotional lability, depressed level of consciousness, performance status decreased).

Gastrointestinal disorders: mesenteric artery thrombosis, colitis ischaemic.

Reproductive system and breast disorders: Peyronie's disease

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis, otitis and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent, practolol. This syndrome has also been reported with timolol maleate.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow card scheme at www.mhra.gov.uk/yellowcard

4.9 Overdose

No specific data are available. Overdosage is unlikely to occur as one 5ml bottle of Timolol Eye Drops 0.25% contains 25 mgs of Timolol 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 timolol 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.)

Paediatric Population:

There is only very limited data available on the use of Timolol (0.25%, 0.25% 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

Topical instillation of 50µl of a 0.25% solution of timolol to the rabbit eye resulted in rapid appearance of timolol in the aqueous humour and to a much lesser degree in the plasma. The concentration in the aqueous humour (mean of 2.47µg/ml) peaked 30 minutes after instillation. The plasma concentration (0.188 µg/ml) also peaked at this time.

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 0.25%, especially in infants and are presumed to increase the risk of side effects such as bronchospasm and bradycardia.

5.3 Preclinical safety data

Acute Toxicity Studies: Data have been reported in a number of animal species. Oral LD_{50} in the mouse and rat are 1137 mg/kg and 1028 mg/kg respectively. Subcutaneous LD_{50} in the mouse and rat are 300 mg/kg and 381 mg/kg respectively.

Chronic Toxicity Studies: No adverse ocular effects were observed with ophthalmic topical administration of timolol in rabbits and dogs in studies lasting one and two years respectively. In studies with oral administration in high doses in dogs and rats, bradycardia and weight increase in the heart, kidneys and liver were observed adverse effects.

Carcinogenicity: In a life-time study in mice, timolol increased the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice when administered orally at doses of 500mg/kg per day, but not at 5 or 50 mg/kg per day. In a 2 year study in rats, oral timolol increased the incidence of adrenal pheochromocytomas in male rats at 300 mg/kg per day but not at 25 or 100 mg/kg per day.

Mutagenicity: Timolol was not shown to be mutagenic when tested in vivo (mouse) in the micronucleus test and cytogenetic assay (at doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 0.1 mg per ml).

Reproduction and fertility: Reproduction and fertility studies in rats have not shown that timolol causes any adverse effects on male or female fertility when administered orally at doses of up to 125 times the maximum recommended human oral dose of 30mg. Studies in rats have shown that timolol at doses of up to 50mg/kg/day (50 times the maximum recommended human oral dose) caused delayed foetal ossification; however there were no adverse effects on post-natal development of offspring. Teratogenic studies in mice and rabbits have not shown that timolol at doses of up to 50 mg/kg/day causes foetal malformations. In mice, timolol at doses of 1000 mg/kg/day (1000 times the maximum recommended human oral dose) was maternotoxic and resulted in an increased incidence of foetal resorptions.

In rabbits, timolol at 100 mg/kg/day (100 times the maximum recommended human oral dose) increased incidence of foetal resorptions but not maternotoxicity.

Timolol maleate 0.25% eye drops have not been adequately studied in human pregnancy. Although timolol eye drops may be absorbed systemically, daily treatment with Timolol Eye Drops 0.25% (1 drop, twice daily in both eyes) will not exceed 0.4mgs timolol compared with the oral therapeutic dose of 20-60 mgs/day.

However as a precautionary measure, it is recommended that timolol should not be used in pregnancy, unless the potential benefit to the pregnant woman exceeds the potential risk to the foetus.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride solution

Disodium edetate

Disodium Hydrogen orthophosphate

Sodium dihydrogen orthophosphate

Sodium chloride

Sodium hydroxide

6.2 Incompatibilities

Benzalkonium chloride may be deposited in soft contact lenses. These lenses should therefore be removed before instillation of the eye drops and not reinserted earlier than 15 minutes after use.

6.3 Shelf life

Unopened: 24months

Opened: 28 days

6.4 Special precautions for storage

Store below 30°C

Protect from light

6.5 Nature and contents of container

10ml & 5ml in Low density polyethylene bottle

6.6 Special precautions for disposal and other handling

Do not touch the dropper tip to any surface as this may contaminate the solution

Close the bottle immediately after use.

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

7. APPLICANT/SUPPLIER

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