Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Timolol 0.5 % w/v Eye Drops, Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: timolol 0.5 % w/v (as timolol maleate).

Excipient:
Benzalkonium chloride 0.01% w/v
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.
Clear, colourless sterile multi-dose eye drops, solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Timolol 0.5% Eye Drops, Solution is indicated for the treatment of open-angle glaucoma, aphakic glaucoma, some patients with secondary glaucoma, and other patients with elevated intraocular pressure who are at sufficient risk to require lowering of their ocular pressure. Timolol 0.5% may be used alone or in combination with other glaucoma medications.

4.2 Posology and method of administration

Apply one drop in the eye(s) twice a day.

Elderly and Paediatric Use:

There are currently no clinical data indicating that dosage modifications are required for use in the elderly.

Safety and effectiveness in children have not been established by adequate and well-controlled studies.

4.3 Contraindications

Timolol 0.5% Eye Drops, Solution is contraindicated in patients with bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second and third degree atrioventricular block; overt cardiac failure; and cardiogenic shock.

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Topically applied beta-blockers can be systemically absorbed. Consequently the same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration.
For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following administration of Timolol.

The following measures are useful after application of the eye drops:
- Keep the eyelid closed for two minutes.
- Close the lacrimal duct with the finger for two minutes.

Patients who are receiving a beta-adrenergic blocking agent orally and Timolol 0.5% should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Timolol 0.5%, alternative therapy should be considered.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol has little or no effect on the pupil.

When Timolol is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

As with the use of other antiglaucoma drugs, diminished responsiveness to Timolol after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least 3 years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

Consideration may be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anaesthesia as beta-blockade reduces the ability of the
heart to respond to beta-adrenergically mediated sympathetic reflex stimuli.

Timolol should not be used while wearing contact lenses as the preservative,
benzalkonium chloride, can be adsorbed by soft contact lenses, discolour them or cause eye irritation. Patients should be advised to remove their contact lenses before instilling Timolol and be instructed to wait 15 minutes before re-inserting their contact lenses

4.5 Interaction with other medicinal products and other forms of interaction

The interactions known for beta-blockers when used orally may also occur with the use of Timolol eye drops.

Although Timolol used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with Timolol and epinephrine has been reported occasionally.

Close observation of the patients 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. Caution should be used in the co-administration of beta-adrenergic agents, such as Timolol and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure and hypotension. In patients with impaired cardiac function, co-administration should be avoided.

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

If supplementary eye preparations are to be used, one should wait about 15 minutes between the two applications.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate and well controlled studies in pregnant women. Timolol 0.5% should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Teratogenicity studies with timolol in mice and rabbits at doses up to 50mg/kg/day (40 times the maximum recommended human oral dose*) showed no evidence of fetal malformations.

* The maximum recommended daily oral dose is 60mg of Timolol. One drop of Timolol 0.5% contains about 1/300 of this dose which is about 0.2 mg.

Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000mg/kg/day (830 times the maximum recommended human oral dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 40 times the maximum recommended human oral dose, in this case without apparent maternotoxicity.

Lactation
Nursing Mothers: Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from Timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

The installation of Timolol may temporarily impair vision. If blurred vision occurs at installation the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Timolol is usually well tolerated. The following adverse reactions have been reported either in clinical trials of up to 3 years duration prior to release in 1978 or since the drug has been marketed:

General disorders and administration site conditions
Headache, asthenia, chest pain.

Cardiac disorders/Vascular disorders
Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, palpitation, cardiac arrest.

Gastrointestinal disorders
Nausea, diarrhea.

Nervous System disorders
Dizziness, increase in objective and subjective symptoms of myasthenia gravis, paresthesia.

Psychiatric disorders
Depression.

Skin and subucutaneous tissue disorders
Hypertenistivity, including localised and generalised rash; urticaria, alopecia.

Respiratory, thoracic and mediastinal disorders
Bronchospasm (predominantly in patients with pre-existing
bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough.

Endocrine disorders
Masked symptoms of hypoglycemia in insulin dependent diabetics.

Eye disorders
Objective and subjective symptoms of ocular irritation, including conjunctivitis,
blepharitis, keratitis, blepharoptosis, decreased corneal sensitivity, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases),
diplopia, ptosis.

Causal Relationship Unknown: The following adverse effects have been reported, and a casual relationship to therapy with Timolol eye drops has not been yet established:

General disorders and administration site conditions
Fatigue.

Cardiac disorders/Vascular disorders
Hypertension, pulmonary edema, worsening of angina pectoris.

Gastrointestinal disorders
Dyspepsia, anorexia, dry mouth.

Nervous System disorders/Psychiatric disorders
Behavioural changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence and other psychic disturbances.

Eye disorders
Aphakic systoid macular edema.

Renal and urinary disorders
Retroperitoneal fibrosis, impotence.

The following additional adverse effects have been reported in clinical experience with oral timolol maleate, and may be considered potential effects of ophthalmic timolol maleate:

General disorders and administration site conditions
Extremity pain, decreased exercise tolerance, weight loss.

Cardiac disorders/Vascular disorders
Edema, worsening of arterial insufficiency, Raynaud’s phenomenon, vasolidation.

Gastrointestinal disorders
Gastrointestinal pain, hepatomegaly, vomiting.

Blood and lymphatic system disorders
Nonthrombocytopenic purpura.

Endocrine disorders
Hyperglycemia, hypoglycemia.

Skin and subcutaneous tissue disorders
Pruritus, skin irritation, increased pigmentation, sweating, cold hands and feet.

Musculoskeletal and connective tissue disorders
Arthralgia, claudication.

Nervous System disorders/Psychiatric disorders:
Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished concentration.

Respiratory, thoracic and mediastinal disorders
Rales, bronchial obstruction.

Ear and labyrinth disorders
Tinnitus.

Eye disorders
Dry eyes.

Renal and urinary disorders
Urination difficulties.

Potential adverse effects: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate:

Gastrointestinal disorders
Mesenteric arterial thrombosis, ischemic colitis.

Blood and lymphatic system disorders
Agranulocytosis, thrombocytopenic purpura.

Nervous system disorders
Reversible mental depression progressing to catatonia; an acute reversible syndrome characterised by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Immune system disorders
Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress.

Renal and urinary disorders
Peyronie's disease

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis and sclerosing serositis attributed to the beta-adrenergic receptor blocking agents, practolol. This syndrome has not been reported with timolol maleate.

4.9 Overdose

A topical overdose with Timolol may be flushed from the eyes by rising abundantly with lukewarm water.

No data are available in regard to overdosage in humans. The oral LD50 of the drug is 1190 and 900 mg/kg in female mice and female rats, respectively.

A. Signs of Overdosage

Overdosage may lead to hypotension, cardiac failure, cardiogenic shock, bradycardia to the extreme of cardiac arrest. In addition respiratory distress, bronchospasms, vomiting, disturbed consciousness and generalized seizures may occur.

B. Treatment of Overdosage

Apart from general measures, monitoring and if necessary, correction of vital signs under intensive care conditions are imperative. Antidotes include:

Atropine:
0.5 to 2mg IV bolus injection

Glucagon:
Initial treatment with 1-10 mg IV, to be followed by 2-2.5 mg/h as continuous drip infusion.

β-sympathomimetic agents according to body weight and (desired) effect; dobutamine, isoprenaline, orciprenaline or adrenaline.

Pacemaker control should be considered in refractory bradycardia.

β2-sympathomimetics (as aerosol or, intravenously, if the aersol effect proves inadequate) or intravenous aminophylline can be used in bronchospasms.

Slow intravenous injection of diazepam is recommended to control seizures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; Antiglaucoma Preparation and Miotics.
ATC Code:S01E D01

Timolol maleate is a $beta_1$ and $beta_2$(non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic direct myocardial depressant or local anesthetic (membrane-stabilizing) activity.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed para-sympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

Timolol, when applied topically in the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

The precise mechanism of the ocular hypotenisve action of Timolol is not clearly established at this time. Tonography and fluorophotometry studies in man suggest that this predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. Unlike miotics, Timolol reduces intraocular pressure with little or no effect on accommodation or pupil size. Thus, changes in visual acuity due to increased accommodation are uncommon and dim or blurred vision and night blindness produced by miotics are not evident. In addition, in patients with cataracts the inability to see around lenticular opacities when the pupil is constricted is avoided.

5.2 Pharmacokinetic properties

The onset of reduction in intraocular pressure following administration of Timolol can usually be detected within one-half hour after a single dose. The maximum effect usually occurs in one to two hours and significant lowering of intraocular pressure can be maintained for periods as long as 24 hours with a single dose. Repeated observations over a period of one year indicate that the intraocular pressure-lowering effect of Timolol is well maintained.

Human plasma pharmacokinetic studies have not been performed with Timolol 0.5% w/v Eye Drops Solution however clinical studies have been performed with similar products. Timolol 0.5% Ophthalmic Solution administered topically once per day for 3 days resulted in maximal plasma concentrations of 0.613 ± 0.281 ng/mL.

These levels were lower than those resulting from well tolerated oral doses. Timolol declined with a half-life of approximately 5 hours.

5.3 Preclinical safety data

Carcinogenicity/Tumorigenicity – In a two-year study of timolol maleate in rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300mg/kg/day (250 times the maximum recommended human oral dose). The maximum recommended single oral dose is 60mg of timolol. One drop of Timolol, 0.5% contains about 1/300 of this dose which is about 0.2mg. Similar differences were not observed in rats administered oral doses equivalent to 20 or 80 times the maximum recommended human oral dose.
In a life-time oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumours and benign uterine polyps in female mice at 500mg/kg/day (approximately 400 times the recommended daily human oral 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, 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 60mg of timolol maleate, the maximum recommended daily human oral dosage, there were no clinically meaningful changes in serum prolactin.

Mutagenicity – 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 µg/mL). In Ames tests the highest concentrations of timolol employed, 5000 or 10,000 µg/plate, were associated with statistically significant elevation 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 to test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction – Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 125 times the maximum recommended human oral dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate
Disodium phosphate dodecahydrate
Benzalkonium chloride
Sodium hydroxide and/or hydrochloric acid (for pH-adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Unopened: 3 years.
After opening: Discard remaining contents four weeks after first opening.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Opaque or natural coloured, low-density polyethylene DROP-TAINER bottle containing 5 ml or 10 ml of solution.
Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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