Summary of Product Characteristics

1. Name of the Medicinal Product

Timolol-POS® 0.5%

Active ingredient: Timolol maleate

2. Qualitative and Quantitative Composition:

1 ml of Timolol-POS® 0.5% solution contains:
Timolol maleate 6.84 mg
(corresponds to 5.0 mg of timolol)

3. Pharmaceutical Form

Eye drops

4. Clinical Particulars

4.1 Therapeutic indications

- Elevated intraocular pressure
- chronic open-angle glaucoma
- aphakic glaucoma
- congenital glaucoma, if other therapeutic regimens are not sufficient

4.2 Posology and method of administration

For ocular use.

Normally, therapy begins with 1 drop of 0.1 % timolol solution twice daily. If required, the dose can be increased to 1 drop of 0.25 % or 0.5 % timolol solution twice daily. Timolol-POS® 0.5% eye drops are instilled into the conjunctival sac and are suitable for long-term therapy.

Concerning the adjustment of the intraocular pressure it has to be noticed that the decrease of pressure can be up to 50% initially and afterwards a tachyphylaxis may occur. The pressure reduction stabilises after 3-12 months. Therefore continuous control of the intraocular pressure is important, above all within the first days of timolol treatment. If oral administration of β-receptor blocking agents occurs, a decrease of intraocular pressure is to be expected. For that reason it must be evaluated if a local treatment on the eye is necessary at all. If there is a systemic administration of β-
Summary of Product Characteristics

receptor blocking agents, the effect of topically applied substances are often less intensive. The decrease of intraocular pressure in patients with highly pigmented iris can be reduced or delayed. Systemic disorders can be reduced by pressing with the finger on the lacrimal duct for about 1 minute after application.

Newborns and infants:
Some cases of apnoea in newborns have been reported, which may have been caused by the immaturity of these patients. Application to premature babies and newborns is not recommended because of the possible central nervous effects. Due to much higher dosages - based on body weight - in newborns and infants, there is a higher chance of systemic side-effects. Therefore, accurate diagnosis is imperative in infants; the patients have to be observed carefully to detect any sign of systemic beta-receptor blockage.

4.3 Contraindications

**Timolol-POS® 0.5%** eye drops are contraindicated in patients with
- bronchial hyperreactivity
- bronchial asthma
- severe chronic obstructive pulmonary disease
- sinus bradycardia
- second and third degree atrio-ventricular block
- overt cardiac failure
- cardiogenic shock
- hypersensitivity to any ingredient of this product
- severe allergic rhinitis or nutritional disorders involving the cornea

Caution is advised with patients suffering from cerebrovascular insufficiency. If a decreased cerebrovascular blood flow is noticed after the treatment with **Timolol-POS® 0.5%** eye drops, an alternative therapy should be considered.

Caution is advised with patients suffering from myasthenia. Under the treatment with timolol-containing eye drops a fortified myasthenia in terms of myasthenic symptoms like double-pictures, hanging eye-lids and general weakness were reported.

4.4 Special warnings and special precautions for use

Benzalkonium chloride can cause irritations on the eye. It may also cause discolouration of soft contact lenses.

Contact lenses should be removed from the eye before applying the eye drops and reinserted again 15 minutes after application.
4.5 Interaction with other medicinal products and other forms of interaction

- the concurrent application of adrenaline-containing eye drops may cause mydriasis.
- timolol’s pharmacologic action of reducing intraocular pressure is enhanced by adrenaline- or pilocarpine-containing eye drops.
- the concurrent systemic use of beta-blockers may lead to a mutual increase in each drug’s pharmacologic activity; intraocular pressure reduction by timolol will be enhanced as well as systemic beta-blocking activity on the cardiovascular system.
- hypotension and bradycardia may be potentiated by the concurrent use of timolol with oral calcium antagonist, digitalis, catecholamine-releasers or beta-blockers.
- The concomitant application of two local ophthalmic beta-receptor blocking agents is not recommended.
- In patients suffering from cardiac insufficiency concomitant application of local beta-receptor blocking agents and oral or intravenous calcium antagonists should be avoided, because A-V conduction defects, left-side heart failure and hypotension may occur.

Benzalkonium chloride accumulates in soft contact lenses. The compound is released from there in a prolonged manner and may damage the cornea.

4.6 Pregnancy and lactation

No well-controlled studies in pregnant women exist. The expected benefit has to be balanced against possible risks. When Timolol-POS® 0.5% eye drops are applied to the mother shortly before delivery bradycardia, hypoglycemia and respiratory depression in the neonate may occur; there are reports about β-blockage in neonates with other β-blockers. Neonates therefore should be observed carefully for several days after delivery.

Lactation: After ocular administration, timolol is secreted into breast milk and may accumulate to higher concentrations than in the mother’s plasma. Although the amount of active ingredient thus received in breast milk is probably of no risk for the newborn, the child should be carefully observed for symptoms of β1-blockade.

4.7 Effects on ability to drive and use machines

Timolol-POS® 0.5% eye drops may cause blurred vision after application even at normal dosages and with proper use. This can subsequently impair reaction time while driving or operating machinery. This is especially relevant in combination with alcohol.

4.8 Undesirable effects

Eyes:
Irritations of the eyes, such as conjunctivitis, blepharitis, keratitis, impaired vision, diplopia, ptosis and sensation of dryness of the eye.
Summary of Product Characteristics

Short term attenuation of the corneal sensitivity as well as lifting of the choroid after fistulectomy is possible.

At the beginning of the treatment headache is possible, which fades after a few days. Allergic reactions to one of the ingredients of Timolol-POS® 0.5% eye drops are possible. Very rare cases of reversible uveitis (uveitis anterior) have been reported in correlation to a product with the same active substance but a different composition and producing process.

Systemic side-effects:
Even under the treatment with eye drops systemic side effects are possible, because timolol is resorbed by the body and reaches the blood circuit. These side effects are rare or very rare.

Cardiovascular system:
Bradycardia, arrhythmia, hypotension, syncope, atroioventricular block, cerebrovascular insult, cerebral ischemia, heart failure, cardiac arrest, palpitations.

Respiratory system:
Bronchospasms (especially in patients with existing broncho-spastic disease), respiratory insufficiency, dyspnea.

Skin:
Hypersensitivities, such as local or general exanthems, urticaria and individual cases alopecia.

Endocrine system:
Covering of symptoms of a hypoglycemia with insuline-dependent patients.

Gastrointestinal tract:
Diarrhoea

Other side-effects:
Headache, weakness, vomiting, giddiness, depression, ear noises (tinnitus), symptoms of Myasthenia gravis, paresthesia, impotence, changes of the hemogram.

Advice: Under the treatment with Timolol-POS® 0.5% eye drops symptoms of a hypoglycaemia may be disguised.

After finishing the treatment the effect of timolol can prolong several days. If the treatment with Timolol-POS® 0.5% eye drops lasted for a longer period of time, the pressure lowering effect may last furthermore for 2-4 weeks. Beta-receptor blocking agents may lower the intraocular pressure in both eyes, even if only one eye was treated. Timolol-POS® 0.5% eye drops is not suitable for patients who have an elevated pressure at night.
Summary of Product Characteristics

Advice:
Like in every treatment of glaucoma the intraocular pressure and the cornea should be examined continuously.

4.9 Overdose

Symptoms of Intoxication:
Overdosing may lead to severe hypotension, cardiac insufficiency, cardiogenic shock, bradycardia up to cardiac arrest. In addition, respiratory disturbances, bronchial spasms, vomiting, confusion, and generalized cramping may occur.

Treatment of Intoxication:
In addition to general measures, vital functions have to be checked and corrected, if necessary, under intensive care conditions. The following antidotes are suitable:

- Atropine: 0.5 - 2 mg as intravenous bolus injection
- Glucagon: Initially 1 - 10 mg intravenously, afterwards 2 - 2.5 mg per hour as infusion
- Beta-sympathomimetic drugs, based on body weight and efficacy: Dobutamine, isoprenaline, orciprenaline, or epinephrine.
- Pace-maker therapy may be indicated in therapy-resistant bradycardia.
- Beta-2-sympathomimetic drugs (as aerosol or, in case of insufficient activity, as injection) or aminophylline, intravenously, can be given in case of bronchial spasm.
- In case of convulsion, slow intravenous application of diazepam is recommended.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

*ATC-Code: S01ED01*

Timolol is a non-selective beta-receptor blocker without intrinsic sympathomimetic activity or local anesthetic (membrane-stabilising) properties. It inhibits β1-receptors, which are localised above all in the heart muscle, as well as β2-receptors. The stimulating effect of catecholamines on the heart is reduced by timolol. In consequence, the neural transmission in the A-V node is decelerated and the systolic discharge is downcasted. The inhibition of β-receptors in the bronchioles leads to an increase of the airway resistance because of a preponderance of the parasymathicus.

Effect on the eye
Timolol eye drops reduce both elevated and normal intraocular pressure. The accurate mechanism of action of timolol by decreasing the intraocular pressure is not known by now. A fluorometric study and tonographic investigations suggest that its effect is based
Summary of Product Characteristics

on a decrease in production of aqueous humor. In some studies a better outflow of aqueous humor could be observed.

The onset of pharmacologic effect is rapid, beginning about 20 minutes after local application to the eye. The maximal reduction of intraocular pressure is reached after one to two hours and a significant decrease in intraocular pressure lasts up to 24 hours.

As in other agents which lower intraocular pressure, long-term use of timolol leads to tachyphylaxis in some patients. However, in a long-term clinical trial, in which 164 patients treated with timolol were studied over 3 years, after intraocular pressures remained stable at their lowered levels.

In contrast to miotics, timolol reduces the intraocular pressure without effecting accommodation or pupil size. This is especially advantageous for cataract patients. If the patient’s therapeutic regimen is changed from miotics to timolol, a correction of refraction may be necessary after the miotic activity subsides.

5.2 Pharmacokinetic properties

Aqueous humour levels:
In rabbits aqueous humour levels of 461 ng/100 mg at maximum were measured 60 minutes after the application of one drop of timolol 1,0%. In men aqueous humour levels of timolol 1 and 2 hours after application of 2 drops of timolol 0,5% amounted 150 ng/100 mg. After 7 hours the level decreased down to 10 ng/100 mg.

Ocular tissue levels:
One drop of a 0.25 % solution of $^{14}$C-marked timolol was applied to a rabbit eye. The maximum radioactivity was detected after 15 - 60 minutes in various ocular tissues. In cornea, nictitating membrane, iris and ciliary body, radioactivities corresponding to between 1 and 10 mg timolol per 100 mg of tissue were measured.

Systemic resorption:
Experiments show that timolol is absorbed systemically after local application to the eye. In a clinical trial, timolol, which is secreted mainly by the kidneys along with its metabolites, was detected in the urine in every patient.

Plasma concentrations:
Plasma concentrations of timolol after local application of the recommended clinical dosages are frequently not detectable (< 2 ng/ml) after either one-time usage or continuous use for 2 weeks. The maximal plasma concentration measured from a dosage of 2 drops twice daily was 9.6 ng/ml. It occurred 30 to 90 hours after the onset of usage.

In some cases, the use of timolol-containing eye drops in newborns and small children leads to a higher plasma concentration than in adults. A three week old infant, who was treated with a 0.25 % timolol-containing eye drop solution at a dosage of one drop twice daily, was found to have a timolol plasma concentration of 34 ng/ml.
5.3 Pre-clinical safety data

a) Acute toxicity:
- See section 4.9 Overdose -

b) Chronic toxicity / Subchronic toxicity:

In studies on rabbits for one year and dogs for two years, topically administered timolol maleate caused no side-effects on the eye. Even the long-term oral administration of high doses of timolol maleate to dogs and rats did not result in side-effects except for bradycardia and an increase in the weight of several organs, in particular, the heart, kidney and liver.

c) Mutagenic and cancerogenic properties:

Detailed data on mutagenicity are not available; all currently available studies are negative.

During a two year study on rats, in which timolol maleate was orally administered at very high doses (300 times higher than the maximal recommended dosage of 1 mg/kg/day for humans), a statistically significant (p<0.05) increase in the rate of pheochromocytoma of the adrenal gland occurred in male rats. In rats administered with 25 to 100 times the maximal recommended dose for humans these types of changes did not occur. In a study on mice, in which timolol was orally administered over their entire life-span, a statistically significant (p<0.05) increase in the rate of benign and malignant lung tumors as well as benign uterine polyps (in female mice) occurred with dosages of 500 mg/kg/day. The increases did not occur, however, with dosages of 5 or 50 mg/kg/day.

Mammary adenocarcinoma rates also increased in the mice receiving very high doses of timolol maleate (500 mg/kg/day). This may be related to an increase in the serum prolactin concentration, which was observed to be increased in the mice receiving 500 mg/kg/day but not in those receiving 5 or 50 mg/kg/day. An increase in the rate of mammary adenocarcinoma in rodents is seen after administration of several substances known to raise serum prolactin concentrations. In adult woman, the oral ingestion of 60 mg of timolol maleate, which is the maximum recommended oral dose for humans, does not raise serum prolactin levels in a clinically significant manner.

Female mice receiving 500 mg/kg/die showed a statistically significant increase in neoplasms.

d) Toxicity on fertility and pregnancy:

Studies on rats showed that the fertility of male and female rats was not adversely effected by doses of timolol up to 150 times greater than the maximum recommended dosage for humans. Experiments investigating the teratogenicity of orally ingested timolol maleate in mice and rabbits showed no evidence of fetal malformations at dosages of up to 50 mg/kg/day. Ossification was sometimes delayed, but this had no
Summary of Product Characteristics

observable effect on postnatal development. Dosages of 1000 mg/kg/day in mice (1000 times the maximal recommended dose for humans) resulted in maternal toxicity as well as in increased rates of fetal resorption. Rabbits receiving 100 mg/kg/day showed similar increased resorption rates but no signs of maternal toxicity.

6. Pharmaceutical Particulars

6.1 List of excipients

Benzalkonium chloride 0.05 mg/ml
Sodium dihydrogen phosphate dihydrate, sodium hydrogen phosphate dodecahydrate, water for injections.

6.2 Incompatibilities

Benzalkonium chloride accumulates in soft contact lenses. The substance is released retarded and can damage the cornea.

6.3 Shelf life

With proper care Timolol-POS® 0.5% eye drops can be used up to 4 weeks after the bottle has been opened.

The duration of stability is 3 years. Timolol-POS® 0.5% eye drops should not be used beyond the expiration date (imprinted on the packaging carton).

6.4 Special precautions for storage

Timolol-POS® 0.5% eye drops should not be stored above 25 °C.

6.5 Nature and contents of container

Polyethylene-bottle with dropping insert and cap containing 5 ml of solution

6.6 Instructions for use/handling

As general rule, contact of the bottle tip with eye or skin surface should be avoided when applying eye drops.

Summary of Product Characteristics

7. **Marketing Authorisation Holder**

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8. **Marketing Authorisation Number**

    N.N.

9. **Date of first Authorisation**

    N.N.

10. **Date of Revision of the Text**

    May 2006