1.5 Product Information

1.5.1 Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
TIMOSOL® 0.5 % w/v eye drops, solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml contains 5 mg of timolol (as timolol maleate)

For full list excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Eye drops, solution.

4. CLINICAL PARTICULARS
4.1.Therapeutic Indications
Reduction of the elevated intraocular pressure in patients with:
- ocular hypertension,
- chronic open angle glaucoma.

4.2.Posology and method of administration
Adults
The initial recommended posology is one drop of timolol maleate 0.25 % in affected the eye(s), twice a day. if the clinical response is not sufficient, the posology can be increased to one drop of 0.50 % solution twice a day in the affected eye(s).

The normalisation of the ocular tension with timolol required sometimes a few weeks, therefore the assessment of the intraocular pressure with the treatment should include 4 weeks period of treatment. Because of the normal nictemeral variation, it is recommended to assess the efficiency of timolol with the measurement of the tension at different times of the day.

In some cases, the daily administration of a single drops can be sufficient, especially when the stabilisation of the intraocular pressure has been reached.

Combination with other treatments
The ophthalmologist may, if found necessary, combine the treatment with TIMOSOL to:
- either a sympatho- or parasympathomimetic anti-glaucomatous eye drops,
- or a systemic treatment with a carbonic anhydrase inhibitor, to obtain a maximal result.

In case TIMOSOL takes on another treatment
- with a beta blocking agent: this eye drops should be stopped at the end of a complete day of treatment, and TIMOSOL should be started the next day,
- with another anti-glaucomatous treatment with a single agent other than a beta blocking agent, overlap the 2 treatments during one day, with a drops of TIMOSOL twice a day. the next day, stop the treatment with the other anti-glaucomatous agent used previously and continue with TIMOSOL.

When TIMOSOL is substituted to multiple combined anti-glaucomatous, the doctor can, on case by case basis, stop some or all the other agents. The suppression should though be done one by one.

When the patients change from myotic agents to TIMOSOL, an examination of the refraction might be necessary when the effects of the myotics have disappeared.

The patient will strictly conform to the medical prescription, that will come with intraocular pressure monitoring, especially during the period of posology adjustment;

Paediatric population
Because of the limitation of the data, timolol can only be recommended for a temporary period, in case of congenital primary glaucoma or juvenile glaucoma, awaiting the decision of surgery or in case of failure of surgery, expecting new options.

Posology
The doctors should assess the benefit/risk ration with great care when a medical treatment with timolol is possible in paediatric patients. Before using timolol, a detailed paediatric anamneses and an examination in order to detect the presence of systemic anomalies should be carried out.
No specific recommendation on posology can be given because of the limited clinical data (see also section 5.1). however, if the benefits are greater than the risks it is recommended to start using the smallest available concentration of active ingredient and only once a day. if the IOP cannot be sufficiently controlled, increasing the dosage to maximum two drops per day and per eye should be considered. In case of two administrations per day, a 12-hour interval should be respected.

Moreover, patient in particular new-born, should be monitored with great care during one to two hours after the first instillation and the side effects at the ocular and systemic levels should be closely monitored until surgery is performed.

Method of administration
The method of administration in children is the same as in adults. In order to limit the potential side effects, a single drop should be instilled at each administration. Also see sections 4.4 and 5.2.

Treatment duration
Temporary treatment in the paediatric population (see section 4.2 “Paediatric population).

4.3. Contraindications
As any medicine containing beta blocking agents, TIMOSOL is contraindicated in patients with:

- Hypersensitivity to the active substance (timolol maleate) or to any excipients listed in section 6.1 and/or to other beta blocking agents.
- Respiratory disorders including bronchial asthma or history of bronchial asthma, severe chronic obstructive pulmonary disease.

- Sinus bradycardia, sinus disease, sinoatrial bloc, second or third degree atrioventricular bloc.
- Confirmed severe cardiac failure, cardiogenic shock.
- Untreated pheochromocytoma.
- Corneal dystrophy: combination with floctafenine (see section 4.5).
- Combination with sulpride (see section 4.5).

4.4. Special warnings and precautions for use

As other ophthalmologic medicines administered locally, timolol maleate is absorbed in the general blood stream. Because of the beta adrenergic activity of timolol maleate, the same types of cardiovascular, pulmonary and other side effects as those observed with general route administration beta blocking agents can occur.
The incidence of the systemic side effects is less frequent and the effects are weaker after ocular administration than general route administration. To reduce the systemic absorption, see below this leaflet.
A decrease in the receptivity to timolol might occur after extended treatment; increasing the dose would be useless. It is required, in long term treatments, to check the absence of "therapeutic escape".

Cardiac disorders
In patients with a cardiovascular disease (for example coronary disease, Prinzmental angina and heart failure) and hypotension, the treatment with beta blocking agents should be assessed critically and a treatment with other substances should be considered.
Patients with cardiovascular diseases should be monitored in order to detect signs of worsening of their disease and of side effects.
Because of their negative dromotropic effect, beta blocking agents should be administered with caution in patients with first degree cardiac bloc.

Vascular disorders
Caution should be exercised in patient with severe peripheral blood stream disorders/diseases (severe form of Raynaud syndrome or disease).

Respiratory disorders
Repiratory reactions, including death caused by bronchospasm in asthmatic patients, have been reported after the administration of certain beta blocking agents by ophthalmic route.
TIMOSOL should be used with caution in patients with mild to moderate chronic obstructive pulmonary diseases (COPD) and only if the potential benefit is greater than the potential risk.

Hypoglycaemia/diabetes
Beta blocking agents should be administered with caution in patients who have spontaneous hypoglycaemia episodes or in patients with unstable diabetes because beta blocking agents might cover the signs and symptoms of acute hypoglycaemia.
Beta blocking agents might also cover signs of hyperthyroidism.
To be used with caution in patient with metabolic acidosis.

Corneal disorders

Ophthalmic beta blocking agents might induce dry eyes. Caution should be exercised in patients with corneal disorders.
Wearing contact lenses requires caution due to the risk of decrease in tear secretion and the related corneal hypoesthesia to beta blocking agents.

Other beta blocking agents
The effect on intraocular pressure or the known systemic effects of beta blocking agents might be potentiated in case of administration of timolol maleate in patients treated with general route beta blocking agents.
The response should be closely monitored in these patients. The combination of 2 local beta blocking agents is not recommended (see section 4.5).

Anaphylactic reactions
During the treatment with beta blocking agents, patients with history of atopy or severe anaphylactic reactions to different allergens might be more sensitive to repeated expositions to these allergens and might not respond to the usual dose of adrenaline to treat anaphylactic reactions.

Choroid detachment
Choroid detachment has been reported during the administration of a treatment targeting the decrease of secretion of aqueous humour (for instance timolol, acetazolamide) after a filtrating surgery.

General anaesthesia
Ophthalmic beta blocking agents might inhibit the beta adrenergic agonist effects, for example, of adrenaline. The anaesthetist should be warned that you use timolol maleate.
Warning should be given to sportsmen, the active ingredient might give a positive result to anti-doping controls.

Paediatric population
Timolol solutions should generally be used with care in young glaucomatous patients (see section 5.2).
It is important to warn the parents of the potential undesirable effects in order for them to immediately stop the treatment. The signs to monitor are cough or wheezing for instance.
Because of the possibility of apnoea and Cheyne-Stokes breathing, this medicine should be used with extreme precaution in new-born, infants and young children. A portable apnoea monitor might be useful in new-born on timolol.

4.5.Interaction with other medicinal products and other forms of interaction
No study of specific interaction has been carried out with timolol maleate.
The use of TIMOSOL is contraindicated in combination with:
1/ Other eye drops
Occasional cases of mydriasis have been reported when administering concomitantly beta blocking agents and adrenaline (epinephrine).
2/ Other medicines
Additive effects causing hypotension and/or bradycardia marked in case of concomitant administration of oral calcium-channel blockers, beta adrenergic blockers, antiarrhythmic

agents (including amiodarone), digitalis, parasympathomimetics, guanethidin with ophthalmic solution of beta blocking agents exist.

Floctafenin
in case of shock or hypotension caused by floctafenin, beta blocking agents inhibit the compensatory cardiovascular mechanism.

Sultopride
Increased risk of ventricular arrhythmia, in particular *torsade de pointe*.
Inhibitors of CYP2D6 (for instance quinidine, SSRIs)
Potentiation of systemic beta adrenergic blocking (for example decrease in heart rhythm, depression) have been reported in case of combination with CYP2D6 inhibitors (for instance quinidine, fluoxetine, paroxetine) with timolol.

4.6.Effects on ability to drive and use machines
Not applicable.

4.6 Fertility, pregnancy and lactation

Pregnancy
No sufficient relevant data exist regarding the use of timolol maleate in pregnant woman.
Timolol maleate should not be used during pregnancy unless absolute necessity, see section 4.2.
Epidemiologic studies did not show any malformation but show a risk of intra uterine delayed growth in case of administration of oral beta blocking agents. Moreover, signs and symptoms of beta adrenergic blocking (for instance bradycardia, hypotension, respiratory distress and hypoglycaemia) were observed in new-born to mother treated with beta blocking agents until delivery.
If TIMOLOL is administered until delivery, the new-born should be closely monitored during the first days of its life.

Breast-feeding
Beta blocking agents are excreted into breast milk. However, at therapeutic dose of timolol maleate contained in the eye drops, it is unlikely that the quantity is sufficient to induce clinical symptoms of beta adrenergic blockage in the breastfed infant. To reduce the systemic absorption, see below this leaflet.

4.7 Effects on ability to drive and use machines

No study related to the effect of this medicine on the ability to drive has been carried out. One should be warned on the potential visual disorders, including refraction modification, diplopia, ptosis, might occur occasionally, as well as frequent episodes of benign and transient blurred vision and less frequent episodes of dizziness and tiredness.

4.8. Undesirable effects
As it is the case with any topical ophthalmological medicine, timolol maleate might pass into the systemic blood stream. This can cause side effects that are similar to those observed with

systemic beta blocking agents. The frequency of the systemic side effects following the local instillation is smaller than this in case of general route administration.
The side effects mentioned include these observed with ophthalmic beta blocking agents.

Immune system disorders
Disseminated lupus erythematosus, systemic allergic reactions including angioedema, urticarial, localised and generalised rash, pruritus, anaphylactic reaction.

Metabolism and nutrition disorders
Hypoglycaemia.

Psychiatric disorders
Insomnia, depression, nightmares, memory loss.

Nervous system disorders
Syncope, stroke, cerebral ischemia, increased signs and symptoms of myasthenia gravis, dizziness, paraesthesia and headaches.

Eye disorders
Signs and symptoms of eye irritation (for instance, burning, tingling, tearing, reddening), blepharitis, conjunctival hyperaemia, conjunctivitis, keratitis, blurred vision and choroid detachment following filtrating surgery (see section 4.4 Special warnings and precautions for use), decrease in corneal sensitivity, dry eye, corneal erosion, corneal hypoesthesia, ptosis and diplopia.

Heart disorders
Bradycardia, chest pains, palpitations, oedema, arrhythmia, congestive heart failure, atrioventricular bloc, cardiac arrest, heart failure, worsening of an arterial stream insufficiency.

Vascular disorders
Hypotension, Raynaud phenomenon, cold hands and feet, claudication.

Respiratory, thoracic and mediastinal disorders
Bronchospasm (especially in patient with pre-existing bronchospastic disease), dyspnoea, cough.

Gastro-intestinal disorders
Dysgueusia, nausea, dyspepsia, dry mouth, abdominal pains, vomiting.

Skin and subcutaneous tissue disorders
Alopecia, psoriasiform eruptions or worsening of a psoriasis, rash.

Musculo-skeletal disorders
Myalgia.

Reproductive organs and breast disorders
Sexual dysfunction (as impotence), decrease in libido, Peyronie syndrome.

General disorders and anomalies at the administration site
Asthenia/tiredness.

Investigations
Antinuclear antibodies positive.
Cases of corneal calcification have been reported rarely with the use of eye drops containing phosphates, in certain patients with significant alteration of the cornea.

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 the national reporting system

4.9.Overdose
No specific data on this preparation is available. The most commonly observed symptoms during an overdose are symptomatic bradycardia, hypotension, bronchospasm and acute heart failure.
If an overdose occurs, the therapeutic measures recommended are the following:
1/ Administration of activated charcoal in case of ingestion. Studies have shown that timolol cannot be eliminated by haemodialysis.
2/ Symptomatic bradycardia: administer 0.25 to 2 mg of atropine sulphate intravenously in order to initiate vagal block. In case of persistence of bradycardia, isoprenaline hydrochloride will be administered cautiously. In resistant cases, the use of a cardiac pacemaker should be considered.
3/ Hypotension: administer a sympathomimetic hypertensive agent as dopamine, dobutamine or noradrenaline. In resistant cases, glucagon hydrochloride has been reported to be useful.
4/ Bronchospasm: use isoprenaline hydrochloride. A concomitant treatment with aminophylline might be considered.
5/ Acute heart failure: the conventional treatment with digitalis, diuretics and oxygen should be established immediately. In resistant cases, the i.v. administration of aminophylline is recommended.
It can be followed, if needed, by the administration of glucagon hydrochloride, that has been reported to be useful in those cases.
6/ Cardiac block: use isoprenaline hydrochloride or a pacemaker.

5. PHARMACOLOGICAL PROPERTIES

5.1.Pharmacodynamic properties
Pharmacological class: beta blocking agents.
ATC-code: S01 ED 01

Timolol maleate, active ingredient of TIMOSOL, is a non-selective beta blocking agent with no significant intrinsic sympathomimetic effect, with direct activity on the myocardia, and showing negligent local membrane-stabilising anaesthetic effect. The action of timolol maleate gets rapidly installed, in about 20 minutes after eye instillation.

The decrease in intraocular pressure reaches its maximum in one to two hours and persists for about 24 hours; this enables the control of the intraocular pressure during the sleep. The exact mode of action of timolol maleate in the reduction of intraocular pressure is not clearly established.
According to some reports, timolol maleate has usually proved to be efficient in a larger number of patient, and has caused fewer side effects and less severe than pilocarpine or adrenaline.
Unlike myotic agents, timolol maleate decreases the intraocular pressure with little or no effect on pupil diameter and accommodation. This is why modifications of visual acuity cause by an increased in accommodation are less frequent. No blurred or weaken vision or night blindness are observed, unlike the treatment with myotic agents. Moreover, the inability to see around the lenticular opacities is prevented in patients with cataract, this happens when the pupil contracts following the use of a myotic agent. When replacing a myotic with timolol maleate, measurement of the refraction is necessary when the effects of the myotic agents have stopped.
As with other anti-glaucomatous agents, a decrease in the response to timolol maleate might appear after prolonged treatment.

Paediatric population
Very few data are available on the use of timolol (0.25 %, 0.5 % one drop twice a day) in the paediatric population for a treatment period up to 12 weeks.
A small clinical trial, double-blinded, randomised, carried out on 105 children (n = 71 on timolol) aged 12 days to 5 years has shown to a certain extent the evidence that timolol is efficient for a short term treatment in the indication of primary congenital glaucoma and primary juvenile glaucoma.

5.2.Pharmacokinetic properties

As with other eye drops, timolol contained in TIMOSOL can pass into the systemic blood stream. The local ophthalmologic installation is thus likely to cause the apparition of beta adrenergic blocking effects.

Paediatric population
As it was confirmed with the data obtained in adults, 80 % of each drop of eye drops passes through the nasolacrimal system, where it is rapidly absorbed in the systemic blood stream through the nasal mucosa, the conjunctiva, the lacrimo-nasal duct, the oropharynx and the intestine, or under the skin that is in contact with a tear.
Because of the blood stream of children is smaller than this of adults, a higher concentration in the blood stream should be taken into account. Moreover, new-born infants have an immature enzymatic metabolic system and this can result in an increased elimination half-life and potential side effects.

Limited data show that the plasma levels of timolol in children after 0.25 % are much greater that those of adults after 0.5 %, especially in infants and are supposed to increase the risk of side effects, as bronchospasm and bradycardia.

5.3.Preclinical safety data
In the rabbit or the dog, in case of eye administration of timolol during 4 weeks, no local side effect was observed.
In the rat, timolol has not been mutagenic and has not altered the fertility.

A carcinotoxicity study has revealed an increase in the incidence of pheochromocytoma in male rats, and of mammary adenoma, of pulmonary tumours and of benign uterine polyps in the mouse, but only in case of use of massive oral doses.

6. PHARMACEUTICAL PARTICULARS

6.1.List of excipients

Disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, disodium edetate, benzalkonium chloride solution, sodium chloride, sodium hydroxide and water for injection.

6.2.Incompatibilities

Not applicable.

6.3.Shelf Life

36 months.

6.4. Special precautions for storage

Store at room temperature (below 30°C). Protect from light. Do not use after one month after the bottle opening.

6.5.Nature and contents of container

The bottle is made of transparent low density polyethylene.
Plastic cap of white low density polyethylene.
Bottle of 5 ml

6.6.Special precautions for disposal and other handling

Bottle opening:

1. With the spike: tighten the cap on the nozzle.
2. The spike in the cap will pierce the tip of the bottle.
3. Dispense drops with gentle pressure. Replace the cap after every use.

7. CATEGORY OF DISTRIBUTION

☐ Other the counter medicine ☒ Prescription only medicine

List I

8. MARKETING AUTHORISATION HOLDER:

Exphar sa
Zoning Industriel de Nivelles Sud, Zone II
Avenue Thomas Edison 105
1402 Thines
Belgium

9. MANUFACTURER:
AHLCON PARENTERALS (INDIA) LIMITED
SP-918, Phase-III, Bhiwadi-301019,
Dist.: Alwar (Rajasthan), India

10. DATE OF REVISION OF THE TEXT
September 2018