SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Timosol 0.50 % eye drops solution

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Eye drops solution.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications

Reduction of intraocular pressure in patients with:
- ocular hypertension
- chronic open-angle glaucoma

4.2. Posology and method of administration

Route of administration
Ophtalmic route.

Posology
Adults
The recommended initial dose is one drop of timolol maleate 0.25% in the affected eye(s) twice daily. If the clinical response is insufficient, the dosage may be increased to one drop of the 0.50% solution twice daily in the affected eye(s).

Normalisation of eye pressure with timolol may take a few weeks, so evaluation of treatment should include determination of intraocular pressure after a treatment period of approximately 4 weeks. Because of normal day-to-day variations in intraocular pressure, the efficacy of timolol is best assessed by measuring pressure at different times of the day.

In a number of cases, the daily administration of a single eye drop may be sufficient, particularly when the intraocular pressure has stabilised.

Combination with other treatments
If deemed necessary, the ophthalmologist may combine treatment with Timosol 0.50 % eye drops, solution:
- with either a sympathomimetic or parasympathomimetic antiglaucoma eye drop,
- or a systemic treatment with a carbonic anhydrase inhibitor, in order to obtain an optimal result.

If Timosol 0.50 % eye drops, solution is to be used to replace another beta-blocker eye drop:
- the beta-blocker eye drop should be discontinued at the end of a full day's treatment and Timosol 0.50 % eye drops, solution
- should be started the next day.
- In the case of another antiglaucoma treatment with a single agent other than a β-blocker, combine the 2 treatments for one day, with one drop of Timosol 0.50 % eye drops, solution

twice a day. The next day, stop treatment with the previous antiglaucoma agent and continue with Timosol 0.50 % eye drops, solution.
- When Timosol 0.50 % eye drops, solution is to substitute more than one antiglaucoma medication, the doctor may decide to discontinue some or all of them, depending on the case. However, only one drug should be discontinued at a time.
- When patients are switched from miotics to Timosol 0.50 % eye drops, solution, a refraction test may be necessary when the effects of the miotics have worn off.

The patient should strictly adhere to the medical prescription, which should be accompanied by monitoring of intraocular pressure, especially during the dosage adjustment period.

Paediatric population
Due to limited data, timolol can only be recommended for a transitional period, in primary congenital or juvenile glaucoma, while a decision is made on a surgical approach and in case of failed surgery while awaiting further options.

Posology
Clinicians should carefully weigh the risks and benefits when considering medical treatment 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 due to limited clinical data (see also section 5.1). However, if the benefit outweighs the risk, it is recommended to use the lowest available active agent concentration once a day. If IOP cannot be sufficiently controlled, a careful uptitration to a maximum of two drops daily per affected eye should be considered. If applied twice daily, an interval of 12 hours should be preferred.

In addition, patients, especially neonates, should be carefully monitored for one to two hours after the first dose at the doctor's office and closely observed for ocular and systemic undesirable effects until surgery is performed.
For paediatric use, the 0.1% active agent concentration may already be sufficient.

Method of administration
The method of administration in children is the same as in adults. In order to limit possible adverse effects, only one drop should be administered with each application. See also sections 4.4 and 5.2.

Duration of treatment
For a transient treatment in the paediatric population (see also section 4.2 'Paediatric population').

4.3. Contraindications

Like all drugs containing beta-blockers, Timosol 0.50 % eye drops, solution is contraindicated in patients with:
- Hypersensitivity to the active substance (timolol maleate) or to any of the excipients listed in section 6.1 and/or other beta-blockers.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker.

- Confirmed heart failure, cardiogenic shock.
- Untreated phaeochromocytoma.
- Corneal dystrophy.
- Association with floctafenine (see section 4.5).
- Association with sultopride (see section 4.5).

4.4. Special warnings and precautions for use

Like other topically applied ophthalmic agents, timolol maleate is absorbed systemically. Due to the beta-adrenergic activity of timolol maleate, the same types of cardiovascular, pulmonary and other undesirable reactions seen with beta-blockers may occur.

Incidence of systemic undesirable effects after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Decreased responsiveness to timolol may occur after prolonged treatment; increasing doses would have no effect. In the case of long-term treatment, there should be an annual check for possible 'resistance to treatment'.

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 treatment with other active substances should be considered.
Patients with cardiovascular diseases should be monitored for signs of deterioration of these diseases and undesirable effects.
Due to their 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 (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.
Timosol 0,50 % eye drops, 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 who are prone to spontaneous hypoglycaemic episodes or in 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.
They should be used with caution in patients with metabolic acidosis.

Corneal conditions
Ophthalmic beta-blockers may induce dry eye. Patients with corneal conditions should be treated with caution.

Contact lens wearers should be carefully monitored because of the risk of decreased lacrimal secretion and corneal hypoesthesia associated with beta-blockers in general.

Other beta-blocking agents
The effect on intraocular pressure or the known effects of systemic beta-blockers may be potentiated when timolol maleate is given to patients already receiving a systemic beta-blocker.
Response should be closely monitored in these patients. The combination of two local beta-blockers is not recommended (see section 4.5).

Anaphylactic reactions
While taking beta-blockers, patients with a 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.

General anaesthesia
Beta-blocker ophthalmological preparations may inhibit the effect of β-adrenergic agonists, e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.
Athletes should be aware that this medicinal product contains an active ingredient that can induce a positive reaction in tests carried out during anti-doping controls.

Paediatric population

Based on the limited data available, the undesirable events profile in children is similar to that in adults. However, there is usually a stronger response to a given stimulus in children than in adults. Irritation may affect compliance to treatment in children.

Timolol solutions should generally be used with caution in young glaucoma patients (see also section 5.2).

It is important to notify parents of potential undesirable effects so they can immediately discontinue treatment. Signs to look for include coughing and wheezing.
Because of the possibility of apnoea and Cheyne-Stokes breathing, this medicine should be used with extreme caution in neonates, infants and young children. A portable apnoea monitor may also be helpful for neonates on timolol.

Excipients with known effect

Timosol 0.50% eye drops, solution contains 0.15 mg of phosphates per drop equivalent to 3.0 mg/ml.

Cases of corneal calcification have been reported very rarely in association with the use of phosphate-containing eye drops in some patients with severely damaged corneas.

Timosol 0.50% eye drops, solution contains 0.00001 ml of benzalkonium chloride per drop.

Benzalkonium chloride is known to cause eye irritation and symptoms of dry eye syndrome and may affect the tear film and surface of the cornea. Caution should be used in dry eye patients and those at risk of corneal damage. Patients should be monitored in the event of prolonged use.

4.5. Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with timolol maleate.
The use of Timosol 0.50 % eye drops, solution is contraindicated in combination with:
1/ Other eye drops
Occasional cases of mydriasis have been reported with concomitant administration of beta-blockers and adrenaline (epinephrine).
2/ Other medicinal products
There is a risk of additive effects resulting in marked hypotension and/or bradycardia with concomitant oral administration of calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis, parasympathomimetics, guanethidine and ophthalmic solutions containing beta-blockers.

Floctafenine
In case of shock or hypotension caused by floctafenine, beta-blockers inhibit compensatory cardiovascular mechanisms.

Sultopride
Increased risk of ventricular arrhythmia, especially torsades de pointes.
CYP2D6 inhibitors (e.g. quinidine, SSRIs)
Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported when CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) are combined with timolol.

4.6. Fertility, pregnancy and lactation

Pregnancy
There are no sufficiently relevant data regarding the use of timolol maleate in pregnant women. Timolol maleate should not be used during pregnancy unless absolutely necessary. To reduce the systemic absorption, see section 4.2.

Epidemiological studies have not revealed any 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 neonates of mothers treated with beta-blockers until delivery.
If TIMOSOL 0.50 % eye drops, solution is administered until delivery, the neonate should be closely monitored during the first days of life.

Breast-feeding
Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol maleate 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 section 4.2.

4.7. Effects on ability to drive and use machines

No studies have been performed on the effects of this medicinal product on the ability to drive.

When driving a vehicle or operating machinery, be aware that visual disturbances including refractive changes, diplopia, and ptosis may occur occasionally, as well as frequent, mild and transient episodes of blurred vision, and less frequent episodes of dizziness or fatigue.

4.8. Undesirable effects

Like other topically applied ophthalmic drugs, timolol maleate can be absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. The incidence of systemic undesirable effects after local instillation is lower than with systemic administration.
The undesirable effects listed include those observed with the ophthalmic beta-blocker class.

Immune system disorders
Systemic lupus erythematosus, 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, hallucination.

Nervous system disorders
Syncope, cerebrovascular accident, cerebral ischemia, increased signs and symptoms of myasthenia gravis, dizziness, paresthesias and headache.

Eye disorders
Signs and symptoms of ocular irritation (e.g. burning, stinging, tearing, redness), blepharitis, conjunctival hyperaemia, conjunctivitis, keratitis, blurred vision and choroidal detachment following filtration surgery (see section 4.4 Special warnings and precautions for use), decreased corneal sensitivity, dry eye, corneal erosion, corneal hypoesthesia, ptosis and diplopia.

Cardiac disorders
Bradycardia, chest pain, palpitations, oedema, arrhythmia, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure, worsening of arterial insufficiency.

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

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 (such as impotence), decreased libido, Peyronie's syndrome.

General disorders and administration site conditions
Asthenia/fatigue.

Investigations
Positive antinuclear antibodies.

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 common symptoms observed during overdosage with beta-blockers are symptomatic bradycardia, hypotension, bronchospasm and acute heart failure.
If an overdose occurs, the following measures are recommended:
1/ Administration of activated charcoal in case of ingestion. Studies have shown that timolol cannot be removed by haemodialysis.
2/ Symptomatic bradycardia: administer intravenous atropine sulphate 0.25-2mg to induce vagal blockade. If bradycardia persists, intravenous isoprenaline hydrochloride should be administered with caution. In refractory cases, the use of a pacemaker should be considered.
3/ Hypotension: administer a hypertensive sympathomimetic such as dopamine, dobutamine or noradrenaline. In refractory cases, the administration of glucagon hydrochloride has proved useful.
4/ Bronchospasm: use isoprenaline hydrochloride. Concomitant treatment with aminophylline may be considered.
5/ Acute heart failure: conventional treatment with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases, i.v. administration of aminophylline is recommended.
This may be followed, if necessary, by the administration of glucagon hydrochloride, which has been reported useful in these cases.
6/ Heart block: use isoprenaline hydrochloride or a pacemaker.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: beta-blocker.
ATC-code: S01ED01

Timolol maleate, the active ingredient in TIMOSOL 0.50 % eye drops, solution, is a non-selective beta-blocker with no significant intrinsic sympathomimetic activity, no direct myocardial activity, and negligible local anaesthetic membrane-stabilising effect. Timolol maleate takes effect rapidly, approximately 20 minutes after instillation into the eye. The reduction in intraocular pressure peaks within one to two hours and persists significantly for approximately 24 hours; this allows intraocular

pressure to be controlled during sleep. The exact mode of action of timolol maleate in reducing intraocular pressure is not clearly established.
There have been reports that timolol maleate has usually been effective in more patients, with fewer and less severe side effects than pilocarpine or adrenaline.
Unlike miotics, timolol maleate reduces intraocular pressure with little or no effect on pupillary diameter and accommodation. Therefore, changes in visual acuity due to increased accommodation are uncommon. There is no blurred or weakened vision or night blindness, as is the case with miotics. In addition, patients with cataracts are not prevented from seeing around lenticular opacities, which occurs when the pupil is constricted by a miotic. When replacing a miotic with timolol maleate, a refraction measurement may be necessary when the effects of the miotic have passed.
As with other antiglaucoma agents, a decrease in response to timolol maleate may occur after prolonged treatment.

Paediatric population
There is only very limited data available on the use of timolol (0.25%, 0.5% one drop twice daily) in the paediatric population for a treatment period up to 12 weeks.
A small, published, double-blind, randomised clinical trial of 105 children (n=71 on timolol) aged 12 days to 5 years showed some evidence that timolol is effective for short-term treatment in the indication of primary congenital and primary juvenile glaucoma.

5.2. Pharmacokinetic properties

As with other eye drops, timolol contained in TIMOSOL 0.50 % eye drops, solution may enter the systemic circulation. Local ocular instillation may therefore result in the onset of the beta-adrenergic blocking effects of timolol.

Paediatric population
As already confirmed by data in adults, 80% of each eye drop passes through the nasolacrimal system, where it can be rapidly absorbed into the systemic circulation via the nasal mucosa, conjunctiva, lacrimonasal duct, oropharynx and intestine, or through the skin from tear overflow.
Due to the fact that the blood volume in children is smaller than in adults, a higher circulation concentration must be taken into account. In addition, neonates have immature metabolic enzyme pathways and this may result in an increased elimination half-life and possible undesirable effects.

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 thought to increase the risk of side effects, such as bronchospasm and bradycardia.

5.3. Preclinical safety data

In rabbits and dogs, when timolol was administered to the eye for 4 weeks, no local side effects were observed.
In rats, timolol was not mutagenic and did not affect fertility.
A carcinogenicity study showed an increased incidence of phaeochromocytoma in male rats, as well as mammary adenocarcinomas, lung tumours and benign uterine polyps in mice, but only when high oral doses were used.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Disodium phosphate, monosodium phosphate, edetate disodium, benzalkonium chloride solution, sodium chloride, sodium hydroxide, water for injections.

6.2. Incompatibilities
Not applicable.

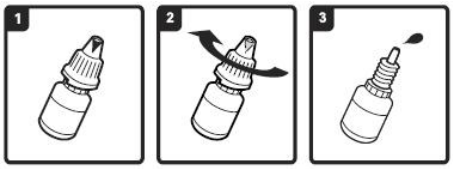
6.3. Shelf life
36 months.
Do not use the eye drops more than 4 weeks after first opening.

6.4. Special precautions for storage
Store at room temperature (below 30°C), away from light.
For storage conditions after first opening, see section 6.3.

6.5 Nature and contents of container
TIMOSOL 0.50 % eye drops solution is available in a 5 ml clear low density polyethylene bottle with a white low density polyethylene plastic cap

6.6. Special precautions for disposal and other handling

Opening the bottle:



1. With the spike: screw the cap tightly onto the bottle nozzle,
2. piercing the bottle nozzle with the spike
3. Dispense the drops with a gentle squeeze of the bottle. Replace the cap after each use.

7. DISPENSING CLASSIFICATION

☐ Not subject to medical prescription ☒ Subject to medical prescription

List I

8. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

Exphar s.a.
Zoning Industriel de Nivelles Sud, zone II
Av. Thomas Edison 105
1402 Thines
Belgium

9. NAME AND ADDRESS OF MANUFACTURER

Ahlcon Parenterals (India) Ltd
SP 917-918, Phase III, Industrial Area
Bhiwadi – 301019, District Alwar
Rajasthan, India

10. DATE OF REVISION OF THE TEXT

06/2022.