Timabak,

eye drop solution
Timolol
0,25 % 0,50 %

1. NAME OF MEDICINAL PRODUCT

0,25 % TIMABAK 0.25%, eye drop solution
0,50 % TIMABAK 0.50%, eye drop solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

0,25 %

Timolol..... 0.250 g
In the form of timolol maleate ..... 0.343 g
For 100 ml of solution

0,50 %

Timolol..... 0.500 g
In the form of timolol maleate ..... 0.685 g
For 100 ml of solution

See section 6.1 for the complete list of excipients.

3. PHARMACEUTICAL FORM

Eye drop solution.
Clear colourless liquid.

4. CLINICAL PARTICULARS

4.1. Clinical indications

Intra-ocular hypertension.
Chronic wide-angle glaucoma.

4.2. Dosage and route of administration

Ophthalmic route.

Dosage

It is recommended to start the treatment by instilling 1 drop of TIMABAK 0.25% in the afflicted eye twice daily.
In cases of insufficient effectiveness, 1 drop of the higher concentration TIMABAK 0.50% should be used twice daily in the afflicted eye.
If they deem necessary, the ophthalmologist can combine TIMABAK with one or more other anti-glaucoma treatments (ocular and/or other route of administration).
However, it is not recommended to combine two beta-blocking eye drop solutions (see section 4.4).
The other eye drop solutions should be administered at least 15 minutes before TIMABAK.
In any case, it may take several weeks before ocular pressure returns to normal with TIMABAK eye drops. An assessment of the treatment should also include measurement of the intraocular eye pressure after approximately 4 weeks of treatment.
In certain cases, a daily administration of just 1 drop of TIMABAK eye drops may prove sufficient, in particular when the intraocular pressure is maintained at satisfactory levels.
The systemic passage may be reduced by nasolacrimal occlusion or by closing the eyelids for 2 minutes. This method may help to reduce systemic side effects and increase local effectiveness.

Replacement of a previous treatment

When TIMABAK is used to replace other anti-glaucoma eye drops, the latter should be stopped at the end of one full day of treatment and TIMABAK should be administered the next day on the basis of 1 drop at 0.25% twice daily in the afflicted eye.
In cases of insufficient effectiveness, switch to TIMABAK 0.50% on the basis of 1 drop in the afflicted eye twice daily.
When TIMABAK substitutes for a combination of anti-glaucoma treatments only one drug at a time should be withdrawn.
When TIMABAK is used to replace myotic eye drops, a refraction test may prove necessary when the effects of the myotic eye drops are no longer apparent.
Upon prescribing the eye drops, an examination of intraocular pressure should be performed, especially at the onset of treatment.

4.3. Contraindications

The contraindications of beta-blockers administered by other routes should be borne in mind, even though systemic effects of beta-blockers have seldom been observed after ocular instillation.

- asthma and chronic obstructive pulmonary disease,
- second and third degree atrioventricular block in the absence of a device,
- poorly controlled heart insufficiency,
- cardiogenic shock,
- Prinzmetal's angina,
- sinus diseases (including sino-auriculaire blocks),
- bradycardia (45-50 contractions per minute),
- Raynaud's disease and peripheral circulatory disturbances,
- untreated phaeochromocytoma,
- hypotension,
- hypersensitivity to one of the components of the medicinal product,
- in combination with floctafenine (see section 4.5),
- in combination with sultopride (see section 4.5).

This drug should not generally be taken in combination with amiodarone, certain calcium antagonists (bepridil, verapamil, diltiazem) and beta-blockers used to treat heart failure. (see section 4.5).

4.4. Particular warnings and precautions for use

As with other eye care medicines administered locally, Timolol is absorbed into the general circulation. Due to Timolol's beta-adrenergic effect, the same cardiovascular, pulmonary and other side effects as those observed with beta-blockers administered internally may occur.
There are fewer occurrences of systemic side effects after ocular instillation than during administration taken internally.
To reduce systemic absorption, see section 4.2.
A reduction in sensitivity may appear in prolonged therapy with Timolol. During long-term treatment drug resistance should be checked annually.

Heart conditions

In patients presenting with cardiovascular conditions (i.e. coronary disease, Prinzmetal's angina and heart failure) and hypotension, treatment with beta-blockers will have to be critically assessed and treatment with other active substances should be considered.
Patients presenting with cardiovascular conditions should be monitored in order to detect any signs of worsening of the condition and side effects.
Given that beta-blockers have a negative dromotropic effect, caution should be exercised when beta-blockers are administered to patients with first-degree heart block.
If the heart rate falls below 50 to 55 beats per minute at rest and the patient shows symptoms linked to bradycardia, the dose should be reduced.

Vascular diseases

Caution is required in patients presenting with severe diseases / disorders of the peripheral circulation (severe forms of Raynaud's syndrome or disease).

Treated phaeochromocytoma

Use of beta-blockers for the treatment of hypertension due to a treated phaeochromocytoma requires careful monitoring of blood pressure.

Respiratory diseases

Respiratory reactions, including death due to bronchospasm in asthmatic patients, have been reported following administration of certain beta-blockers via the ophthalmic route.
TIMABAK must be used with caution in patients presenting with mild or moderate chronic obstructive pulmonary disease (COPD), and only in cases where the potential benefit outweighs the potential risk.

Hypoglycaemia/diabetes

Beta-blockers must be administered with caution in patients subject to spontaneous hypoglycaemia or presenting with labile diabetes as the beta-blockers may mask the signs and symptoms of acute hypoglycaemia.
Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases

Ophthalmic beta-blockers may cause dry eyes. Caution should be exercised in patients presenting with corneal diseases.

Contact lenses:

There is a risk of intolerance to contact lenses due to the reduction in tear secretion, linked to beta-blockers in general.

Other beta-blockers

The effect on intraocular pressure or the known effects of systemic beta-blockers can be potentiated where Timolol is administered to patients already taking beta- blockers internally.
The response must be closely monitored in these patients. It is not recommended to combine two local beta-blockers (see section 4.5).

Anaphylactic reactions

During treatment with beta-blockers, patients with a history of atopia or severe anaphylactic reaction to various allergens may have a higher sensitivity to repeated exposure to these allergens and may not respond to the usual adrenaline dosage used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported during administration of a treatment to reduce the secretion of aqueous humour (i.e. timolol, acetazolamide) following filtration surgery.

Psoriasis

There have been reports of exacerbation of psoriasis in patients undergoing beta-blocker therapy and care should be taken in prescribing it.

General anaesthesia

Ophthalmic beta-blockers may inhibit the effects of ß adrenergic agonists, i.e. adrenaline. The anaesthetist must be notified that the patient is being treated with timolol.

Elderly patients, with renal and/or liver failure

These subjects are at risk and when beta-blocking eye drops are administered systemically, adjustment of the dosage is often required.

Athletes

The attention of sports professionals is drawn to the fact that this medicinal product contains an active ingredient which can induce a positive reaction in anti-doping tests.

0,50 % This medicinal product contains 0.361 mg of phosphates per drop, equivalent to 11.28 mg/mL.

0,25 % This medicinal product contains 0.407 mg of phosphates per drop, equivalent to 12.7 mg/mL

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

Eye drops

Ophthalmologic surveillance is necessary in cases of concomitant treatment with adrenaline-containing ophthalmic solution (risk of mydriasis).

Other medicinal products

Even though the amount of beta-blockers passing into the systemic circulation after ocular instillation is low, a risk of drug interaction exists.
The interactions observed after administration of beta-blockers by other routes should be taken into consideration.

Contraindicated combinations

- **Floctafenine**

In the case of shock or hypotension due to floctafenine, reduction of compensatory cardiovascular reactions by the beta-blockers.

- **Sultopride**

Increased risk of ventricular arrhythmias, and torsades de pointes in particular.

Combinations to be avoided

- **Amiodarone**

Contractility, automatism and conduction disorders, (suppression of compensatory sympathetic mechanisms).

- **Calcium antagonists (Bepridil, Diltiazem and Verapamil)**

Automatism disorders (excessive bradycardia, sinus arrest), sinoauricular atrioventricular conduction disorders and heart failure (synergy of effects).
This type of combination should be given under close ECG and clinical surveillance, particularly in elderly patients or those at the start of treatment.

- **Beta-blockers used in cases of heart failure**

Risk of increased side effects due to the beta-blockers, with a particular risk of excessive bradycardia.

Combinations requiring the exercise of caution

- **Volatile halogenated anaesthetics**

Reduction of compensatory cardiovascular reactions by beta-blockers. (beta-adrenergic inhibition may be suppressed by beta-stimulants during operations).
As a general rule, do not discontinue beta-blocker therapy and in any case, avoid abrupt discontinuation. Notify the anaesthetist of the treatment.

- **Anticholinesterases: Donepezil, galantamine, rivastigmine, neostigmine, pyridostigmine, tacrine, ambenonium**

Risk of excessive bradycardia (increase in bradycardia symptoms)
Regular clinical monitoring.
Potentiation of the systemic beta-blocker effects of the eye drop solution and an increase in the plasma concentrations of the beta-blocker have been reported when **combining ophthalmic beta-blockers and quinidine**, probably due to quinidine inhibition of beta-blocker metabolism (described for timolol).

- **Baclophene**

Increase in the antihypertensive effect.
Blood pressure should be monitored and the dosage of antihypertensive drugs should be adjusted if necessary.

- **Clonidine and other central antihypertensive agents (alphamethyldopa, guanfacine, moxonidine, rilmenidine)**

Significant rise in blood pressure in cases of abrupt discontinuation of treatment by the central antihypertensive agent.
Avoid abrupt discontinuation of the central antihypertensive agent. Clinical monitoring.

- **Insulin, hypoglycaemic sulphamides**

1. All beta-blockers can mask certain symptoms of hypoglycaemia e.g.

palpitations and tachycardia.
2. Most non-cardioselective beta-blockers increase the incidence and severity of hypoglycaemia.

Patients should be cautioned and increase self-examination of the blood especially at the onset of treatment.

- **Drugs inducing torsades de pointes**

Antiarrhythmics of Class Ia (quinidine, hydroquinidine, disopyramide) and class III (amiodarone, dofetilide, ibutilide, sotalol), some neuroleptics: phenothiazinics (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamides (amisulpride, sulpiride, tiapride), butyrophenone (droperidol, haloperidol), other neuroleptics (pimozide) and other medicinal products such as: bepridil, cisapride, diphemanil, erythromycine IV, vincamine IV, mizolastine, halofantine, sparfloxacine, pentamidine, moxifloxacine, etc.
Increased risk of ventricular arrhythmias, and torsades de pointes in particular.
Clinical and electrocardiographical monitoring.

- **Propafenone**

Contractility, automatism and conduction disorders, (suppression of compensatory sympathetic mechanisms).
Clinical and electrocardiographical monitoring.

Combinations to be considered carefully

- **NSAIDs (taken internally) including cox-2 selective inhibitors**

Decrease in the antihypertensive effect (inhibition of vasodilatory prostaglandins by NSAIDS and salt and water retention by pyrazol-containing NSAIDS).

- **Alpha-blockers for urological treatments: alfuzosin, doxazosin, prazosin, tamsulosin, terazosin**

Increase in the hypotensive effect. Risk of increased orthostatic hypotension.

- **Amifostine**

Increase in the antihypertensive effect.

- **Calcium antagonists (dihydropyridines)**

Hypotension, heart failure in patients with latent or poorly controlled cardiac insufficiency (in vitro negative inotropic effect of dihydropyridines, more or less pronounced depending on the product and liable to add to the negative inotropic effects of beta-blockers). Concomitant treatment with beta-blockers can also minimise sympathetic reflex reaction which takes place in the case of excessive haemodynamic repercussion.

- **Imipramine (tricyclic) antidepressants, neuroleptics**

Antihypertensive effect and increased risk of orthostatic hypotension (additive effect).

- **Mefloquine**

Risk of excessive bradycardia (increase in bradycardia symptoms)

4.6 Fertility, pregnancy and lactation

Pregnancy

Relevant data on the use of timolol in pregnant women is not sufficiently available. Timolol must not be used during pregnancy except in cases of absolute necessity. To reduce systemic absorption, see section 4.2.
Epidemiological studies have not reported any malformation effects but do show a risk of intrauterine growth restriction in cases of oral administration of beta-blocker agents. In addition, signs and symptoms of beta-adrenergic blocking (e.g. bradycardia, hypotension, respiratory difficulties and hypoglycaemia) have been observed in the newborns of mothers treated with beta-blockers up to delivery. If TIMABAK is administered up to delivery, the newborn must be closely monitored during the first few days of life.

Breast-feeding

Beta-blockers pass into breast milk. However, at the therapeutic doses of timolol found in the eye drops, it is unlikely that sufficient quantities will be present in the breast-milk to induce clinical symptoms of beta-adrenergic blockade in the neonate. To reduce systemic absorption, see section 4.2.
Breast-feeding is not advised if treatment with Timabak is necessary.

4.7. Effects on aptitude to drive vehicles or to operate machines

No studies have been carried out on the effects of this medicinal product on the ability to drive.
However, visual disturbances including refractive changes, diplopia, ptosis, blurred vision, together with dizziness may occur and affect the ability to drive or use machines.
If these effects occur, the patient should wait until symptoms subside before driving or using machines.

4.8. Side effects

As with other eye care medicines administered locally, Timolol is absorbed into the general circulation. This may cause side effects similar to those observed with systemic beta-blockers. There are fewer occurrences of systemic side effects after local instillation than during administration taken internally.
The cited side effects include the effects observed with the ophthalmic class of beta-blockers.

Immune system diseases
Systemic lupus erythematosus, systemic allergic reactions including angio oedema, hives, local and widespread rash, pruritis, anaphylactic reaction.

Metabolic and nutrition disorders
Hypoglycaemia.

Psychiatric conditions
Insomnia, depression, nightmares, loss of memory, hallucinations.

Nervous system diseases
Syncope, strokes, cerebral ischemia, increase in signs and symptoms of myasthenia gravis, dizziness, paresthesia and headaches.

Ocular diseases
Signs and symptoms of ocular irritation (e.g. burning sensation, stinging, watery eyes, redness), blepharitis, conjunctival hyperaemia, conjunctivitis, keratitis, blurred eyesight and choroïdal detachment following filtration surgery (see section 4.4 Particular warnings and precautions for use), decrease in corneal sensitivity, dry eyes, corneal erosion, ptosis, diplopia, blurred eyesight including refractive changes (sometimes due to stopping treatment with myotics).

Heart diseases
Bradycardia, chest pains, palpitations, oedema, arrhythmia, congestive heart failure, bloc atrioventricular block, cardiac arrest, heart failure.

Vascular diseases
Hypotension, Raynaud's disease, cold hands and feet, claudication.

Respiratory thoracic and mediastinal disorders
Bronchospasm (especially in patients presenting with a pre-existing bronchospastic disease), dyspnea, coughing.

Gastro-intestinal disorders
Dysgeusia, nausea, dyspepsia, diarrhea, dry mouth, abdominal pain, vomiting.

Skin and subcutaneous tissue disorders
Alopecia, psoriasis-like eruptions or worsening of an outbreak of psoriasis, rash.

Musculoskeletal and systemic disorders
Myalgias.

Disorders of reproductive organs and breasts
Sexual disorders, loss of libido, impotence.

General disorders and anomalies at the site of administration
Asthenia/fatigue.

Investigations
Positive antinuclear antibodies.
A few rare cases of corneal calcification have been reported in combination with the use of drops containing phosphates in patients with severely damaged corneas.

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. Overdosage

Even though the amount of beta-blockers passing into the systemic circulation after ocular instillation is low, a risk of overdose should be borne in mind. The symptoms and course of action are identical to those of an overdose of beta-blockers taken internally.
No specific data for this preparation are available. The most common side effects observed during overdose with beta-blocking agents are symptomatic bradycardia, hypotension, bronchospasm and acute heart failure.
In case of overdose, the following measures should be envisaged:

1 - Gastric lavage, if ingested. Studies have shown that timolol does not dialyse readily.
2 - Symptomatic bradycardia: administer atropine sulphate intravenously at a dose of 0.25 to 2 mg, so as to induce vagal blockade. If bradycardia persists, intravenous isoprenaline hydrochloride should be administered cautiously. In refractory cases, the use of a cardiac pacemaker should be considered.
3 - Hypotension: administer a sympathomimetic agent such as dopamine, dobutamine or norepinephrine. In refractory cases, the use of glucagon hydrochloride has been shown to be useful.
4 - Bronchospasm: isoprenaline hydrochloride should be used. Concomitant therapy with aminophylline may be considered.
5 - Acute heart failure: conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases, the use of intravenous aminophylline is recommended. This may be followed, if necessary, by administration of glucagon hydrochloride which has been shown to be useful.

Heart block: isoprenaline hydrochloride or a pacemaker should be used.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

BETA-BLOCKER, ATC Code: **S01ED01**.
«The eye drops are without preservative and are presented in a multi-dose bottle equipped with a device containing a membrane filter (0.2 microns) in order to protect them from microbial contamination during the period of use.»

General:
Timolol can be characterised by three pharmacological properties:
- Non-cardioselective beta-blocker,
- Absence of partial agonist capacity [or absence of intrinsic sympathomimetic activity (ISA)],
- non-significant stabilising effect on membranes (local anaesthetic or quinidine-like).

Ocular:
- Timolol maleate eye drops lower intraocular pressure which may or may not be in association with glaucoma;
- Its action is visible about 20 minutes after instillation, reaches a maximum in 1 to 2 hours and is still present after 24 hours;
- The hypotensive effect stabilizes with time and may remain constant for one year. A reduction in the level of sensitivity to timolol maleate is quite possible, notably after prolonged treatment.
- There is practically no change in the diameter of the pupil or in accommodation.

5.2. Pharmacokinetic properties

In a study of plasma concentrations of the drug in six patients, systemic exposure to timolol was determined following administration of timolol 0.50% twice daily. Average plasma concentrations after the morning dose were 0.46 ng/ml and 0.35 ng/ml after the afternoon dose.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, Water for injections

6.2. Incompatibility

Not applicable.

6.3. Shelf life

2 years
After first-time opening of the bottle, the eye drop solution can be kept for up to 8 weeks.

6.4. Special precautions for storage

Store at a maximum temperature of 25°C.

6.5. Nature and contents of the outer package

5 ml bottle (PE) with dropper, equipped with an anti-microbial filter (polyethersulfone) and a medium (LDPE).
10 ml bottle (PE) with dropper, equipped with an anti-microbial filter (polyethersulfone) and a medium (LDPE).
Not all the presentations may be marketed.

6.6. Particular precautions for disposal and handling

No particular requirements.

7. PRODUCT OWNER

Laboratoires THEA
12, rue Louis Bleriot
63017 Clermont-Ferrand Cedex 2
France

8. DATE OF REVISION OF THE TEXT

November 2019

9. DOSIMETRY

Not applicable.

10. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

CONDITIONS FOR PRESCRIPTION AND ISSUE
List I.

Théa

NREG438C5L01/0722