Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Timofluid 1 mg/g eye gel in single-dose container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains 1 mg of timolol as timolol maleate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye gel in single-dose container.
Opalescent, colourless to slightly yellow gel.

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

Ocular use.
Adults
The recommended dosage regimen is 1 drop of Timofluid 1 mg/g in the affected eye (or eyes), once a day, in the morning.

Elderly:
There has been wide experience with the use of timolol eye drops in elderly patients. The dosage recommendations given above reflect the clinical data derived from this experience.

Children and adolescents
There is no experience in children and adolescents. This eye gel is therefore not recommended in such patients.
If the ophthalmologist considers it necessary, Timofluid 1 mg/g may be combined with one or more other anti-glaucoma treatments (local and/or systemic route of administration).
However, the combination of two beta-blocker eye drops is not recommended (see section 4.4.).
The other eye drops should be administered at least 15 minutes before Timofluid 1 mg/g. The eye gel should be the last medication instilled.

Nonetheless, response to Timofluid 1 mg/g may take several weeks to stabilise intraocular pressure, therefore the monitoring of the treatment should include intraocular pressure assessment after a treatment period of approximately four weeks.

Method of administration
Timolol eye gel should be instilled into the conjunctival sac.
A single-dose contains enough gel to treat both eyes.
For single use only.

Patients should be instructed:
- to avoid contact between the dropper tip and the eye or eyelids,
- to use the eye gel immediately after first opening the single-dose container and to discard the single-dose after use.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

Replacement of a previous treatment:

When Timofluid 1 mg/g is used to replace another anti-glaucoma eye drops, this eye drops should be discontinued after a full day of therapy, and Timofluid 1 mg/g should be started the next day at the dosage of one drop in the affected eye (or eyes) once a day, in the morning.

If Timofluid 1mg/g is replacing a combination of anti-glaucoma treatments, only one drug should be withdrawn at a time.
If the anti-glaucoma drug being replaced is not a beta-blocker eye drops, it should be continued and one drop of Timofluid 1 mg/g should be instilled in the affected eye (or eyes), once a day. The following day, stop taking the previous drug completely.
When Timofluid 1 mg/g is used to replace miotic eye drops, testing of refraction may prove necessary when the effects of the miotics have disappeared.
Medical prescription should be combined with the monitoring of intraocular pressure, particularly when the treatment is initiated.

4.3 Contraindications

As with all products containing beta-receptor blocking agents, Timolol is contraindicated in patients with:

- Hypersensitivity to the active substance (timolol maleate) or to any of the excipients listed in section 6.1,
- 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,
- Overt cardiac failure, cardiogenic shock,
- Untreated pheochromocytoma,
- Corneal dystrophies.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic agents timolol maleate is absorbed systemically. Due to betaadrenergic component, timolol maleate, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur.
Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see 4.2.
As with any glaucoma treatment, regular examination of the intraocular pressure and cornea is recommended.

If Timofluid 1 mg/g is administered to reduce intraocular pressure in patients with closed-angle glaucoma, a miotic should be used in combination.
In such patients, the immediate objective of the treatment is to reopen the angle, which requires the use of a miotic agent in order to obtain pupil constriction, since timolol maleate has little or no effect on the pupil.

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 the therapy with other active substances should be considered.
Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.
Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.
The dosage should be reduced if the rate falls below 50-55 beats per minute at rest, and if the patient presents bradycardia-related symptoms.
Beta-blockers may increase the risk of rebound hypertension.

Vascular disorders
Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Treated pheochromocytoma
These patients should not receive β-blocking agents without concomitant α-adrenoceptor blocking therapy.

Respiratory disorders
Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic betablockers.
Timofluidshould 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 subject to spontaneous hypoglycaemia or to 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.

Metabolic disease
It should be used with caution in patients with metabolic acidosis.

Corneal diseases
Ophthalmic β -blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Patients wearing contact lenses
There is a risk of intolerance to contact lenses due to a beta-blocker induced reduction in lacrimal secretion.
Timolol eye gel has not been studied in patients using contact lenses, and therefore the wearing of contact lenses should be avoided while using Timofluid.

Other beta-blocking agents
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol maleate is given to the patients already receiving a systemic beta-blocking agent.
The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5).

Anaphylactic reactions
While taking beta-blockers, patients with 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.

Psoriasis
Beta-blockers have been reported to aggravate psoriasis and its use in this condition therefore deserves careful consideration.

Withdrawal of therapy
As with systemic beta-blockers, if discontinuation of ophthalmic timolol is needed in patients with coronary heart disease, therapy should be withdrawn gradually.

Elderly patients, impaired renal and/or hepatic function
When such agents are administered orally in such high-risk subjects, a dosage adjustment is often necessary.

Surgical anaesthesia

β-blocking ophthalmological preparations may block systemic β-agonist effects e.g. of adrenaline. The anaesthetist should be informed when the patient is receiving timolol maleate.

Sportsmen
Sportsmen should be warned that this drug contains an active substance, which may induce a positive analytical result in anti-doping controls.

4.5 Interaction with other medicinal products and other forms of interactions

No specific drug interaction studies have been performed with timolol maleate.
Although the quantity of beta-blockers, which passes into the systemic circulation is low after ocular instillation, the risk of drug interactions is still present.
It is therefore advisable to keep in mind the interactions observed with beta-blockers given by general route.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, betaadrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

Potentiated systemic betablockade (e.g., decreased heartrate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

Combinations which are not recommended (see section 4.4)

+ **Bepridil**
Automatism disorders (excessive bradycardia, sinus arrest), sinoatrial and atrioventricular conduction disorders and increased risk of ventricular rhythm disorders (torsades de pointes) as well as cardiac failure.
This combination should only take place under close clinical and ECG monitoring, particularly in elderly subjects or in those beginning treatment.

+ **Diltiazem**
Automatism disorders (excessive bradycardia, sinus arrest) sinoatrial and atrioventricular conduction disorders and cardiac failure.
This combination should only take place under close clinical and ECG monitoring, particularly in elderly subjects or those starting treatment.

+ Verapamil
Automatism disorders (excessive bradycardia, sinus arrest) sinoatrial and atrioventricular conduction disorders and cardiac failure.
This combination should only take place under close clinical and ECG monitoring, particularly in elderly subjects or those starting treatment.

+ Fingolimod
Potentiation of bradycardic effects can have fatal consequences. Beta-blockers are more at risk that they prevent adrenergic compensation mechanism.
Continuous clinical and ECG monitoring during 24 hours after the first dose.

Combinations requiring precautions for use

+ Amiodarone
Automatism and conduction disorders (suppression of compensatory sympathetic mechanisms).
Clinical and ECG monitoring is recommended.

+ Class I antiarrhythmics (except lidocaine)
Contractility, automatism and conduction disorders (suppression of compensatory sympathetic mechanisms).
Clinical and ECG monitoring is recommended.

+ Volatile halogenated anaesthetic agents
Reduction in compensatory cardiovascular mechanisms by beta-blockers. Beta-adrenergic inhibition may be counteracted during surgery by beta-mimetics.
As a general rule, do not discontinue beta-blocker therapy, and in any event, avoid a sudden discontinuation. The anaesthetist should be advised of this treatment.

+ Baclofen
Enhancement of hypotension risk, notably orthostatic.
Blood pressure monitoring and, if necessary, dosage adjustment of the antihypertensive.

+ Central anti-hypertensives
Significant increase in arterial pressure if treatment with a central anti-hypertensive is suddenly discontinued.
Avoid sudden withdrawal of treatment with a central anti-hypertensive. Clinical monitoring.

+ Insulin, oral hypoglycaemic agents ; Glinides ; Gliptines
All beta-blockers may mask certain symptoms of hypoglycaemia: palpitations and tachycardia.
Warn the patient and, particularly at the beginning of treatment, self-monitoring of glycaemia by the patient should be increased.

+ Lidocaine
With lidocaine used intravenously: increase in plasmatic concentrations of lidocaine with a possibility of adverse neurological and cardiac side effects (reduction in hepatic clearance of lidocaine).
Clinical and ECG monitoring and possibly testing of the plasmatic concentrations of lidocaine during the combined therapy and after the beta-blocker has been withdrawn. Adaptation if necessary of dosage regimen of lidocaine.

+ Drugs which may cause torsades de pointes
Enhanced risk of ventricular arrhythmia, particularly torsades de pointes.
Clinical and ECG monitoring is recommended.

+ Propafenone
Contractility, automatism and conduction disorders (suppression of compensatory sympathetic mechanisms).
Clinical and ECG monitoring is recommended.

Combinations to be taken into account

+ Alpha-blockers intended for urological use; Anti-hypertensive alpha-blockers
Enhancement of hypotensive effect. Increased risk of orthostatic hypotension.

+ Amifostine
Enhancement of hypotension risk, notably orthostatic.

+ Imipraminic antidepressants
Enhancement of hypotension risk, notably orthostatic.

+ Neuroleptic
Enhancement of hypotension risk, notably orthostatic. Vasodilatator effect and risk of hypotension, notably orthostatic (additional effect).

+ Non-steroidal anti-inflammatory drugs
Reduction in the antihypertensive effect (inhibition of vasodilator prostaglandins by non-steroidal anti-inflammatory drugs and of water and salt retention by phenylbutazone).

+ Other bradycardial drugs
Risk of excessive bradycardia (additive effects).

+ Dihydropyridines
Hypotension, cardiac failure in patients with latent or uncontrolled cardiac insufficiency (additional negative inotropic effects). Moreover, the beta-blocker can minimise the sympathetic reflex reaction, which comes into play in the event of excessive haemodynamic repercussion.

+ Dipyridamole
With the dipyridamole by intravenous route: enhancement of the anti-hypertensive effect.

+ Pilocarpine (for systemic use)
Risk of excessive bradycardia (additive bradycardial effects).

+ Nitro derivatives and related
Enhancement of hypotension risk, notably orthostatic.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data for the use of timolol maleate in pregnant women. Timolol maleate should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see 4.2.

Epidemiological studies have not revealed 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 betablockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If Timofluid 1 mg/g is administered until delivery, the neonate should be carefully 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 4.2.

Fertility
Timolol maleate has not been found to have any effect on fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Timofluid has minor influence on the ability to drive and use machines.
No studies on the effect of this medicinal product on the ability to drive have been conducted. While driving vehicles or operating different machines, it should be taken into account that occasionally visual disturbances may occur including refractive changes, diplopia, ptosis, frequent episodes of mild and transient blurred vision and occasional episodes of dizziness or fatigue.

4.8 Undesirable effects

Like other topically applied ophthalmic drugs, timolol maleate is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic betablocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

Immune system disorders:
Systemic lupus erythematosus, systemic allergic reactions including angiocœdema, urticaria, localised and generalised rash, pruritus, anaphylactic reaction.

Metabolism and nutrition disorders:
Hypoglycaemia.

Psychiatric disorders:
Depression, insomnia, nightmares, memory loss,hallucination.

Nervous system disorders:

Syncope, cerebrovascular accident, cerebral ischemia, increase in signs and symptoms of myasthenia gravis, dizziness, paraesthesia, and headache.

Eye disorders:
Signs and symptoms of ocular irritation, (e.g. burning, stinging, itching, tearing, redness), blepharitis, conjunctival hyperaemia, conjunctivitis, keratitis, blurred vision, and choroidal detachment following filtration surgery (see 4.4 Special warnings and special precautions for use), decreased corneal sensitivity, dry eyes, corneal erosion, ptosis, diplopia, refractive changes (due to withdrawal of miotic therapy in some cases).

Cardiac disorders:
Bradycardia, chest pain, palpitations, oedema, arrhythmia, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure, claudication.

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

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, libido decreased, impotence.

General disorders and administration site conditions:
Asthenia/fatigue.

Investigations:
Antinuclear antibodies positive.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No data specific to this preparation are available. The most common side effects caused by beta-blocker overdosage are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiovascular insufficiency.

If overdosage occurs, the following measures should be considered:
1. Administration of activated charcoal, if the preparation has been taken orally. Studies have shown that timolol maleate cannot be removed by haemodialysis.
2. Symptomatic bradycardia: Atropine sulphate, 0.25 to 2 mg intravenously, should be used 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: A sympathomimetic agent such as dopamine, dobutamine or noradrenaline should be given. In refractory cases, the use of glucagon has been useful.
4. Bronchospasm: Isoprenaline hydrochloride should be given. Concomitant therapy with aminophylline may be considered.

5. Acute cardiac 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 glucagon, which has been found useful.
Heart blocks: Isoprenaline hydrochloride or a pacemaker should be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : *ANTIGLAUCOMA PREPARATIONS AND MIOTICS;* Beta-blocking agents
ATC code: S01ED01

General:
Timolol can be characterised by three pharmacological properties:
- non-cardioselective beta-blockade
- partial agonist potential [moderate intrinsic sympathomimetic activity (ISA)]
- non-significant membrane stabilising effect (local anaesthetic or quinidine-like)

Ocular:
- timolol maleate eye gel reduces intra-ocular pressure, whether or not this is associated with glaucoma
- an effect is seen around 20 minutes following instillation, reaches a maximum in 1 to 2 hours and is still present after 24 hours
- there is no effect on pupil diameter or visual acuity

5.2 Pharmacokinetic properties

Timofluid 1 mg/g eye gel is a preservative free formulation.

Negligible systemic exposure has been observed in patients treated with Timofluid 1 mg/g eye gel given once daily. Data from a recent comparative pharmacokinetic study (LOQ = 0.146 ng/ml) have shown that the plasma level is generally below the LOQ.

5.3 Preclinical safety data

None of the mutagenesis studies carried out *in vivo* and *in vitro* on timolol have produced any evidence of mutagenic potential. Cancerogenic potential in timolol has been shown in animals, at exposure levels much higher than those observed in clinical practice during treatment with Timofluid 1 mg/g.

Reprotoxicity studies have not shown any teratogenic effect in mice, rats and rabbits. In rats, a delay in ossification was observed at levels of exposure much higher than those observed in clinical practice during treatment with Timofluid 1 mg/g. No effects on fertility were observed in rats.

In rabbits, a single or repeated instillation of Timofluid 1mg/g for 28 days did not cause any local or systemic intolerance, nor local anaesthetic effect.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol
Polyvinyl alcohol
Carbomer 974 P
Sodium acetate trihydrate
Lysine monohydrate
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.
After opening of the single-dose container: use immediately and discard the single-dose container after use.
After opening of the sachet: use the single-dose containers within 1 month.

6.4 Special precautions for storage

Keep the single-dose containers in the sachet and the outer carton in order to protect from light.

6.5 Nature and contents of container

10 single-dose containers (PEBD) containing 0.4 g of gel are packed in sachet (paper/aluminium), box of 3 or 9 sachets.

A pack size contains 30 (3x10) or 90 (9x10) single-dose containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA1107/003/001

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