Safeguarding public health

MHRA

Public Assessment Report

Timolol 0.25%w/v Eye Drops
PL 23097/0001

Timolol 0.5%w/v Eye Drops
PL 23097/0002

Medicines and Healthcare products Regulatory Agency

TIMOLOL 0.25%w/v EYE DROPS
PL 23097/0001

TIMOLOL 0.5%w/v EYE DROPS
PL 23097/0002

UKPAR

TABLE OF CONTENTS

TIMOLOL 0.25%w/v EYE DROPS
PL 23097/0001

TIMOLOL 0.5%w/v EYE DROPS
PL 23097/0002

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted The Swiss Group Limited Marketing Authorisations (licences) for the medicinal products Timolol 0.25%w/v Eye Drops (PL 23097/0001) and Timolol 0.5%w/v Eye Drops (PL 23097/0002). These are prescription only medicines [POMs] for treating increased pressure in the eye.

The products contain the active ingredient timolol maleate. In the eye, timolol reduces raised and normal eye pressure by blocking the production of the watery fluid known as aqueous humour.

These are simple abridged applications that cross-refer to previously granted licences for Timolol Eye Drops 0.25% (PL 15872/0001) and Timolol Eye Drops 0.5% (PL 15872/0002).

No new or unexpected safety concerns arose from these simple applications and it was therefore judged that the benefits of using Timolol 0.25%w/v Eye Drops and Timolol 0.5%w/v Eye Drops outweigh the risks, hence Marketing Authorisations have been granted.

TIMOLOL 0.25%w/v EYE DROPS
PL 23097/0001

TIMOLOL 0.5%w/v EYE DROPS
PL 23097/0002

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

INTRODUCTION

The UK granted marketing authorisations for the medicinal products Timolol 0.25%w/v Eye Drops (PL 23097/0001) and Timolol 0.5%w/v Eye Drops (PL 23097/0002) to The Swiss Group Limited on 10 July 2006 and 17 July 2006 respectively. The products are prescription only medicines [POMs].

These applications were submitted as simple abridged applications according to Article 10.1(a)i of Directive 2001/83/EC, as amended, cross-referring to Timolol Eye Drops 0.25% (PL 15872/0001) and Timolol Eye Drops 0.5% (PL 15872/0002), approved in the UK on 9 August 2000.

The products contain timolol maleate. Timolol is a non-selective β-adrenergic blocker, which does not possess significant intrinsic sympathomimetic or local anaesthetic (membrane-stabilising) activity. When applied topically in the eye, it reduces both elevated and normal intraocular pressure by inhibiting the production of aqueous humour.

No new data were submitted for these simple applications, nor were any necessary, as the data were identical to that of the previously granted cross-referenced products. As the cross-referenced products were granted prior to the introduction of current legislation, no public assessment reports were generated for them.

Timolol 0.25%w/v Eye Drops and Timolol 0.5%w/v Eye Drops are used in the reduction of elevated intraocular pressure in conditions such as ocular hypertension, chronic open-angle glaucoma (including aphakic patients), and some cases of secondary glaucoma.

PHARMACEUTICAL ASSESSMENT

LICENCE NUMBER:	**PLs 23097/0001-2**
PROPRIETARY NAME:	**Timolol 0.25%w/v Eye Drops (PL 23097/0001)** **Timolol 0.5%w/v Eye Drops (PL 23097/0002)**
ACTIVE INGREDIENT:	**Timolol maleate Ph.Eur.**
COMPANY NAME:	**The Swiss Group Ltd.**
LEGAL STATUS:	**POM**

INTRODUCTION

These are two simple abridged applications, submitted under Article 10.1(a)(i) of Directive 2001/83/EC (as amended) for timolol eye drops in two strengths, 0.25%w/v and 0.5% w/v. The reference products are Timolol Eye Drops 0.25% (PL 15872/0001) and Timolol Eye Drops 0.5% (PL 15872/0002) held by FDC International Ltd, granted 9 August 2000.

A letter of access has been provided by the applicant.

Written confirmation that the manufacturer is prepared to manufacture the product on the applicant's behalf is provided.

Written confirmation that the applicant has the Quality Module in their possession is provided.

EXPERT REPORTS

Satisfactory statements are provided.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
LABELLING
PATIENT INFORMATION LEAFLET (PIL)

Satisfactory.

RECOMMENDATION

Grant of a Marketing Authorisation is acceptable.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.

CLINICAL ASSESSMENT

No new clinical data have been supplied with these applications and none are required for applications of this type.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The data for these applications are consistent with those previously assessed for the cross-referenced products and as such have been judged to be satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

These applications are identical to previously granted applications for Timolol Eye Drops 0.25% and Timolol Eye Drops 0.5%.

No new or unexpected safety concerns arose from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of the cross-referenced products.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-referenced products. Extensive clinical experience with the active ingredient timolol is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.

TIMOLOL 0.25%w/v EYE DROPS
PL 23097/0001

TIMOLOL 0.5%w/v EYE DROPS
PL 23097/0002

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation applications for Timolol 0.25%w/v Eye Drops and Timolol 0.5%w/v Eye Drops on 27 July 2005.
2	Following standard checks, the MHRA informed the applicant that its application was considered valid on 5 October 2005.
3	The MHRA's assessment of the submitted data was completed on 19 October 2005.
4	Further information was requested from the company on 20 October 2005.
5	The applicant submitted its response to further information request in a letter dated 16 March 2006.
6	The MHRA completed its assessment of the application on 7 July 2006.
7	The application for Timolol 0.25%w/v Eye Drops was determined on 10 July 2006.
8	The application for Timolol 0.5%w/v Eye Drops was determined on 17 July 2006.

TIMOLOL 0.25%w/v EYE DROPS
PL 23097/0001

TIMOLOL 0.5%w/v EYE DROPS
PL 23097/0002

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Timolol 0.25% w/v Eye Drops

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient

Timolol (as maleate) 0.25% w/v

3 PHARMACEUTICAL FORM

Eye Drops, solution
For excipients, see 6.1.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of elevated intraocular pressure in conditions such as:
- Ocular hypertension;
- Chronic open-angle glaucoma (including aphakic patients);
- Some cases of secondary glaucoma

4.2 Posology and method of administration

Adults and children over 12 years: recommended therapy is one drop of Timolol Eye Drops in the affected eye(s) twice a day.

Elderly: Dosage need not be modified for the elderly as there has been wide experience with the use of Timolol Eye Drops in elderly patients.

Children below the age of 12 years: This product is currently not recommended for use.

It is recommended that therapy is initiated using Timolol 0.25% Eye Drops. If the clinical response is not adequate, the dosage may be increased to one drop of Timolol 0.5% Eye Drops in each affected eye twice daily. Intraocular pressure should be reassessed approximately four weeks after starting treatment because response to Timolol Eye Drops may take a few weeks to stabilise. Provided that intraocular pressure is maintained at satisfactory levels, many patients can then be placed on once daily therapy.

If necessary, concomitant treatment with miotics, epinephrine and/or carbonic anhydrase inhibitors can be instituted. In order to prevent the active substance(s) from being washed out when additional ophthalmic medication is used, an interval of at least 10 minutes between each application is recommended. The use of two topical beta-adrenergic agents is not recommended.

Transfer from other topical beta-blocking agents: Discontinue use after a full day of therapy and start treatment with Timolol Eye Drops the next day, with one drop in each affected eye twice daily.

Transfer from a single antiglaucoma agent other than a topical beta-blocking agent: Continue the agent and add one drop of Timolol Eye Drops in each affected eye twice daily. On the following day, discontinue the previous agent completely, and continue with Timolol Eye Drops.

4.3 Contraindications

- Cardiogenic shock;
- Overt cardiac failure;
- Second and third degree AV block;
- Sinus bradycardia;
- Presence or history of bronchial asthma;
- Presence or history of severe chronic obstructive pulmonary disease;
- Severe peripheral circulatory disturbances (Raynaud disease);
- Hypersensitivity to any of the ingredients or to other beta-blocking agents.

4.4 Special warnings and precautions for use

Timolol Eye Drops may be absorbed systemically and adverse reactions seen with oral beta-blockers may occur. Patients who are receiving a beta-adrenergic blocking agent orally as well as Timolol Eye Drops should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Cardiac failure should be adequately controlled before beginning therapy with Timolol Eye Drops. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure. Respiratory and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death associated with cardiac failure have been reported.

Timolol Eye Drops should be used with caution in patients with sick sinus syndrome, Prinzmetal's angina, untreated phaeochromocytoma, metabolic acidosis, hypertension and diabetics under treatment (timolol may mask the signs of and response to hypoglycaemia).

Risk from 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, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

This formulation of Timolol Eye Drops contains benzalkonium chloride as a preservative which may be deposited in soft contact lenses. Hence, Timolol Eye Drops should not be used while wearing these lenses. The lenses should be removed before instillation of the drops and not reinserted earlier than 15 minutes after use.

When Timolol Eye Drops is used to reduce intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

A reduction in ocular hypotensive response has been reported in some patients following prolonged therapy with Timolol eye drops.

Muscle weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalised weakness). Timolol Eye Drops have been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop any intercurrent ocular condition (e.g. trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of present multi-dose container.

There have been reports of bacterial keratitis associated with the use of topical ophthalmic products.

4.5 Interaction with other medicinal products and other forms of interaction

Although Timolol Eye Drops alone has little or no effect on pupil size, mydriasis has occasionally been reported when Timolol is given with adrenaline.

The effect on intraocular pressure or the known effects of systemic beta-blockade such as hypotension or bradycardia may be exaggerated when Timolol Eye Drops is given to patients already receiving an oral beta-blocking agent. The response of these patients should be closely monitored.

As Timolol Eye Drops may be absorbed systemically, the following interactions seen with oral beta-blockers may occur:

Calcium channel blockers (verapamil and diltiazem): negative effect on contractility and atrio-ventricular conduction can lead to cardiac failure and hypotension.

Digitalis glycosides: in association with calcium channel blockers may increase atrio-ventricular conduction time.

Catecholamine-depleting drugs (rauwolfia alkolids, reserpine etc): potentiation of hypotension and/or marked bradycardia.

Clonidine: increased risk of "rebound hypertension" on discontinuation of clonidine.

Class I anti-arrhythmic drugs (eg disopyramide, quinidine) and amiodarone: potentiation of bradycardia, sinus arrest and AV block.

Anaesthetic drugs: increased risk of myocardial depression and hypotension due to blockade of cardiac response to reflex sympathetic stimuli.

Cimetidine, hydralazine, phenothiazines and alcohol: may increase plasma level of timolol.

4.6 Pregnancy and lactation

Timolol Eye Drops has not been studied in human pregnancy. However, timolol may cross the placenta with the potential to cause adverse effects of beta-blockade e.g. bradycardia in the foetus and neonate. Timolol Eye Drops should therefore not be used in pregnancy unless the potential benefit to the pregnant woman justifies the potential risk to the foetus.

Timolol Eye Drops may be systemically absorbed and excreted in the breast milk, with the potential to cause adverse effects related to beta-blockade in the infant. Treatment during breast feeding is therefore not recommended unless the potential benefit to the nursing mother justifies the potential risk both to the infant and to the mother.

4.7 Effects on ability to drive and use machines

There are currently no data available on the effects of Timolol Eye Drops on the ability to drive or use machinery. It has to be taken into account that dizziness, fatigue, transient ocular irritation, blurred vision and lacrimation may occur occasionally.

4.8 Undesirable effects

Timolol Eye Drops are usually well tolerated. The following adverse reactions have been reported:

Body as a whole:	Headache, asthenia, fatigue, chest pain.
Cardiovascular:	Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischaemia, congestive cardiac failure, palpitations, cardiac arrest, oedema, claudication, Raynaud's phenomenon, cold hands and feet.
Digestive:	Nausea, diarrhoea, dyspepsia, dry mouth.
Nervous system/:	Dizziness, depression, insomnia, nightmares, memory loss, increase in signs and symptoms of myasthenia gravis, paraesthesia.
Skin:	Hypersensitivity including localised and generalised rash, urticaria, alopecia, exacerbation of psoriasis.
Respiratory:	Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnoea, nasal congestion, cough.
Endocrine:	Masked symptoms of hypoglycaemia in insulin-dependent diabetics.
Special senses:	Signs and symptoms of ocular irritation, including burning and stinging, conjunctivitis, blepharitis, keratitis, blepharoptosis, decreased corneal sensitivity, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis, choroidal detachment following filtration surgery.

The following adverse effects have been reported, and a causal relationship to therapy with timolol eye drops has not been established:

Cardiovascular:	Hypertension, pulmonary oedema, worsening of angina pectoris;
Digestive:	anorexia;
Nervous system/Psychiatric:	Behavioural changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence and other psychic disturbances;
Special Senses:	Aphakic cystoid macular oedema;
Others:	Retroperitoneal fibrosis, impotence, pseudopemphigoid.

The following additional adverse effects have been reported in clinical experience with oral timolol maleate, and may be considered potential effects of ophthalmic timolol maleate:

Body as a whole:	Extremity pain, decreased exercise tolerance, weight loss;
Cardiovascular:	Oedema, worsening of arterial insufficiency, Raynaud's phenomenon, vasodilation;
Digestive:	Gastrointestinal pain, hepatomegaly, vomiting;
Haematologic:	Nonthrombocytopenic purpura;
Endocrine:	Hyperglycaemia, hypoglycaemia;
Skin:	Pruritis, skin irritation, increased pigmentation, sweating, cold hands and feet:

Musculoskeletal: Arthralgia, claudication;
Nervous System/Psychiatric: Vertigo, local weaknesses, decreased libido, nightmares, insomnia, diminished concentration;
Respiratory: Rales, bronchial obstruction;
Special Senses: Tinnitus, dry eyes;
Urogential: Urination difficulties.

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate:

Digestive: Mesenteric arterial thrombosis, ischaemic colitis;
Haematologic: Agranulocytosis, thrombocytopenic purpura;
Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterised by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium and decreased performance on neuropsychometrics;
Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress;
Urogenital: Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent, practolol. This syndrome has been reported with timolol maleate.

4.9 Overdose

No specific data are available. Overdosage is unlikely to occur as one 5ml bottle contains 12.5 mg (Timolol Eye Drops 0.25%) or 25mg (Timolol Eye Drops 0.5%) of timolol maleate compared with the usual adult oral dose of 20-60 mg per day.

However, in the rare event that overdosage occurs the most common signs and symptoms to be expected following overdosage with a beta-adrenergic receptor blocking agent are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure. If overdosage does occur, the following measures should be considered:

1 Gastric lavage, if ingested. Studies have shown that timolol cannot be easily removed by hemodialysis.
2 Symptomatic bradycardia: Atropine sulphate, 0.25 to 2mg 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 may be considered.
3 Hypotension: A sympathomimetic pressor agent such as dopamine, dobutamine or noradrenaline should be used. In refractory cases, the use of glucagon has been reported to be useful.
4 Bronchopasm: Isoprenaline hydrochloride should be used. Additional 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 suggested. This may be followed, if necessary, by glucagon which has been reported to be useful.

6 Heart block (second or third degree): Isoprenaline hydrochloride or a pacemaker should be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: S01ED01 Ophthalmological beta-blocking agent

Timolol is a non-selective β-adrenergic blocker, which does not possess significant intrinsic sympathomimetic or local anaesthetic (membrane-stabilising) activity. When applied topically in the eye, it reduces both elevated and normal intraocular pressure by inhibiting the production of aqueous humour.

Unlike miotics, Timolol reduces intraocular pressure with little or no effect on pupil size or accommodation.

The onset of reduction in intraocular pressure following ocular administration of timolol can be detected within 30 minutes after a single dose The maximum effect usually occurs in one to three hours and significant lowering of intraocular pressure can be maintained for as long as 24 hours following a single dose.

If systemically absorbed, as is possible, Timolol maleate is capable of producing beta-blockade elsewhere in the body with consequent systemic effects (increased airway resistance, bradycardia, hypotension etc.)

5.2 Pharmacokinetic properties

Topical instillation of 50µl of a 0.5% solution of timolol to the rabbit eye resulted in rapid appearance of timolol in the aqueous humour and to a much lesser degree in the plasma. The concentration in the aqueous humour (mean of 2.47µg/ml) peaked 30 minutes after instillation. The plasma concentration (0.188 µg/ml) also peaked at this time.

Following topical instillation in humans, the timolol concentration in aqueous humour was 8-100 ng/ml within the first hour while the mean plasma concentration was approximately 1 ng/ml within the first few hours (compared with plasma concentrations of 5-50 ng/ml seen with therapeutic doses of oral timolol).

5.3 Preclinical safety data

Acute Toxicity Studies: Data have been reported in a number of animal species. Oral LD_{50} in the mouse and rat are 1137 mg/kg and 1028 mg/kg respectively. Subcutaneous LD_{50} in the mouse and rat are 300 mg/kg and 381 mg/kg respectively.

Chronic Toxicity Studies: No adverse ocular effects were observed with ophthalmic topical administration of timolol in rabbits and dogs in studies lasting one and two years respectively. In studies with oral administration in high doses in dogs and rats, bradycardia and weight increase in the heart, kidneys and liver were observed adverse effects.

Carcinogenicity: In a life-time study in mice, timolol increased the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice when administered orally at doses of 500mg/kg per day, but not at 5 or 50 mg/kg per day. In a 2 year study in rats, oral timolol increased the incidence of adrenal pheochromocytomas in male rats at 300 mg/kg per day but not at 25 or 100 mg/kg per day.

Mutagenicity: Timolol was not shown to be mutagenic when tested in vivo (mouse) in the micronucleus test and cytogenetic assay (at doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 0.1 mg per ml).

Reproduction and fertility: Reproduction and fertility studies in rats have not shown that timolol causes any adverse effects on male or female fertility when administered orally at doses of up to 125 times the maximum recommended human oral dose of 30mg. Studies in rats have shown that timolol at doses of up to 50mg/kg/day (50 times the maximum recommended human oral dose) caused delayed foetal ossification; however there were no adverse effects on post-natal development of offspring. Teratogenic studies in mice and rabbits have not shown that timolol at doses of up to 50 mg/kg/day causes foetal malformations. In mice, timolol at doses of 1000 mg/kg/day (1000 times the maximum recommended human oral dose) was maternotoxic and resulted in an increased incidence of foetal resorptions.

In rabbits, timolol at 100 mg/kg/day (100 times the maximum recommended human oral dose) increased incidence of foetal resorptions but not maternotoxicity.

Timolol maleate 0.25% eye drops have not been adequately studied in human pregnancy. Although timolol eye drops may be absorbed systemically, daily treatment with Timolol Eye Drops 0.25% (1 drop, twice daily in both eyes) will not exceed 0.4mgs timolol compared with the oral therapeutic dose of 20-60 mgs/day. However as a precautionary measure, it is recommended that timolol should not be used in pregnancy, unless the potential benefit to the pregnant woman exceeds the potential risk to the foetus.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Disodium edetate
Disodium phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate
Sodium chloride
Water for injection

6.2 Incompatibilities

Benzalkonium chloride may be deposited in soft contact lenses. These lenses should therefore be removed before instillation of the eye drops and not reinserted earlier than 15 minutes after use.

6.3 Shelf life

Unopened: 24 months
Opened: 28 days

6.4 Special precautions for storage

Do not store above 25^{o}C
To avoid contamination do not touch dropper tip to any surface.

6.5 Nature and contents of container

Low density polyethylene bottle with polystyrene spiked cap containing 5ml of solution.

6.6 Special precautions for disposal

None stated

7 MARKETING AUTHORISATION HOLDER

The Swiss Group Ltd
2nd Floor Manfield House
1 Southampton St
London WC2R 0LR
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 23097/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/07/2006

10 DATE OF REVISION OF THE TEXT

10/07/2006

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Timolol 0.5% w/v Eye Drops

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient

Timolol (as maleate) 0.5% w/v

3 PHARMACEUTICAL FORM

Eye Drops, solution
For excipients, see 6.1.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of elevated intraocular pressure in conditions such as:
- Ocular hypertension;
- Chronic open-angle glaucoma (including aphakic patients);
- Some cases of secondary glaucoma

4.2 Posology and method of administration

Adults and children over 12 years: recommended therapy is one drop of Timolol Eye Drops in the affected eye(s) twice a day.

Elderly: Dosage need not be modified for the elderly as there has been wide experience with the use of Timolol Eye Drops in elderly patients.

Children below the age of 12 years: This product is currently not recommended for use.

It is recommended that therapy is initiated using Timolol 0.25% Eye Drops. If the clinical response is not adequate, the dosage may be increased to one drop of Timolol 0.5% Eye Drops in each affected eye twice daily. Intraocular pressure should be reassessed approximately four weeks after starting treatment because response to Timolol Eye Drops may take a few weeks to stabilise. Provided that intraocular pressure is maintained at satisfactory levels, many patients can then be placed on once daily therapy.

If necessary, concomitant treatment with miotics, epinephrine and/or carbonic anhydrase inhibitors can be instituted. In order to prevent the active substance(s) from

being washed out when additional ophthalmic medication is used, an interval of at least 10 minutes between each application is recommended. The use of two topical beta-adrenergic agents is not recommended.

Transfer from other topical beta-blocking agents: Discontinue use after a full day of therapy and start treatment with Timolol Eye Drops the next day, with one drop in each affected eye twice daily.

Transfer from a single antiglaucoma agent other than a topical beta-blocking agent: Continue the agent and add one drop of Timolol Eye Drops in each affected eye twice daily. On the following day, discontinue the previous agent completely, and continue with Timolol Eye Drops.

4.3 Contraindications

- Cardiogenic shock;
- Overt cardiac failure;
- Second and third degree AV block;
- Sinus bradycardia;
- Presence or history of bronchial asthma;
- Presence or history of severe chronic obstructive pulmonary disease;
- Severe peripheral circulatory disturbances (Raynaud disease);
- Hypersensitivity to any of the ingredients or to other beta-blocking agents.

4.4 Special warnings and precautions for use

Timolol Eye Drops may be absorbed systemically and adverse reactions seen with oral beta-blockers may occur. Patients who are receiving a beta-adrenergic blocking agent orally as well as Timolol Eye Drops should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Cardiac failure should be adequately controlled before beginning therapy with Timolol Eye Drops. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure. Respiratory and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death associated with cardiac failure have been reported.

Timolol Eye Drops should be used with caution in patients with sick sinus syndrome, Prinzmetal's angina, untreated phaeochromocytoma, metabolic acidosis, hypertension and diabetics under treatment (timolol may mask the signs of and response to hypoglycaemia).

Risk from 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, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

This formulation of Timolol Eye Drops contains benzalkonium chloride as a preservative which may be deposited in soft contact lenses. Hence, Timolol Eye Drops should not be used while wearing these lenses. The lenses should be removed before instillation of the drops and not reinserted earlier than 15 minutes after use.

When Timolol Eye Drops is used to reduce intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

A reduction in ocular hypotensive response has been reported in some patients following prolonged therapy with Timolol eye drops.

Muscle weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalised weakness). Timolol Eye Drops have been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop any intercurrent ocular condition (e.g. trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of present multi-dose container.

There have been reports of bacterial keratitis associated with the use of topical ophthalmic products.

4.5 Interaction with other medicinal products and other forms of interaction

Although Timolol Eye Drops alone has little or no effect on pupil size, mydriasis has occasionally been reported when Timolol is given with adrenaline.

The effect on intraocular pressure or the known effects of systemic beta-blockade such as hypotension or bradycardia may be exaggerated when Timolol Eye Drops is given to patients already receiving an oral beta-blocking agent. The response of these patients should be closely monitored.

As Timolol Eye Drops may be absorbed systemically, the following interactions seen with oral beta-blockers may occur:

Calcium channel blockers (verapamil and diltiazem): negative effect on contractility and atrio-ventricular conduction can lead to cardiac failure and hypotension.

Digitalis glycosides: in association with calcium channel blockers may increase atrio-ventricular conduction time.

Catecholamine-depleting drugs (rauwolfia alkolids, reserpine etc): potentiation of hypotension and/or marked bradycardia.

Clonidine: increased risk of "rebound hypertension" on discontinuation of clonidine.

Class I anti-arrhythmic drugs (eg disopyramide, quinidine) and amiodarone: potentiation of bradycardia, sinus arrest and AV block.

Anaesthetic drugs: increased risk of myocardial depression and hypotension due to blockade of cardiac response to reflex sympathetic stimuli.

Cimetidine, hydralazine, phenothiazines and alcohol: may increase plasma level of timolol.

4.6 Pregnancy and lactation

Timolol Eye Drops has not been studied in human pregnancy. However, timolol may cross the placenta with the potential to cause adverse effects of beta-blockade e.g. bradycardia in the foetus and neonate. Timolol Eye Drops should therefore not be used in pregnancy unless the potential benefit to the pregnant woman justifies the potential risk to the foetus.

Timolol Eye Drops may be systemically absorbed and excreted in the breast milk, with the potential to cause adverse effects related to beta-blockade in the infant. Treatment during breast feeding is therefore not recommended unless the potential benefit to the nursing mother justifies the potential risk both to the infant and to the mother.

4.7 Effects on ability to drive and use machines

There are currently no data available on the effects of Timolol Eye Drops on the ability to drive or use machinery. It has to be taken into account that dizziness, fatigue, transient ocular irritation, blurred vision and lacrimation may occur occasionally.

4.8 Undesirable effects

Timolol Eye Drops are usually well tolerated. The following adverse reactions have been reported:

Body as a whole:	Headache, asthenia, fatigue, chest pain.
Cardiovascular:	Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischaemia, congestive cardiac failure, palpitations, cardiac arrest, oedema, claudication, Raynaud's phenomenon, cold hands and feet.
Digestive:	Nausea, diarrhoea, dyspepsia, dry mouth.
Nervous system/:	Dizziness, depression, insomnia, nightmares, memory loss, increase in signs and symptoms of myasthenia gravis, paraesthesia.
Skin:	Hypersensitivity including localised and generalised rash, urticaria, alopecia, exacerbation of psoriasis.
Respiratory:	Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnoea, nasal congestion, cough.
Endocrine:	Masked symptoms of hypoglycaemia in insulin-dependent diabetics.
Special senses:	Signs and symptoms of ocular irritation, including burning and stinging, conjunctivitis, blepharitis, keratitis, blepharoptosis, decreased corneal sensitivity, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis, choroidal detachment following filtration surgery.

The following adverse effects have been reported, and a causal relationship to therapy with timolol eye drops has not been established:

Cardiovascular:	Hypertension, pulmonary oedema, worsening of angina pectoris;
Digestive:	anorexia;
Nervous system/Psychiatric:	Behavioural changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence and other psychic disturbances;
Special Senses:	Aphakic cystoid macular oedema;
Others:	Retroperitoneal fibrosis, impotence, pseudopemphigoid.

The following additional adverse effects have been reported in clinical experience with oral timolol maleate, and may be considered potential effects of ophthalmic timolol maleate:

Body as a whole:	Extremity pain, decreased exercise tolerance, weight loss;
Cardiovascular:	Oedema, worsening of arterial insufficiency, Raynaud's phenomenon, vasodilation;
Digestive:	Gastrointestinal pain, hepatomegaly, vomiting;
Haematologic:	Nonthrombocytopenic purpura;
Endocrine:	Hyperglycaemia, hypoglycaemia;
Skin:	Pruritis, skin irritation, increased pigmentation, sweating, cold hands and feet:
Musculoskeletal:	Arthralgia, claudication;
Nervous System/Psychiatric:	Vertigo, local weaknesses, decreased libido, nightmares, insomnia, diminished concentration;
Respiratory:	Rales, bronchial obstruction;
Special Senses:	Tinnitus, dry eyes;

Urogential:	Urination difficulties.

In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate:

Digestive:	Mesenteric arterial thrombosis, ischaemic colitis;
Haematologic:	Agranulocytosis, thrombocytopenic purpura;
Nervous System:	Reversible mental depression progressing to catatonia; an acute reversible syndrome characterised by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium and decreased performance on neuropsychometrics;
Allergic:	Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress;
Urogenital:	Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent, practolol. This syndrome has been reported with timolol maleate.

4.9 Overdose

No specific data are available. Overdosage is unlikely to occur as one 5ml bottle contains 12.5 mg (Timolol Eye Drops 0.25%) or 25mg (Timolol Eye Drops 0.5%) of timolol maleate compared with the usual adult oral dose of 20-60 mg per day.

However, in the rare event that overdosage occurs the most common signs and symptoms to be expected following overdosage with a beta-adrenergic receptor blocking agent are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure. If overdosage does occur, the following measures should be considered:

1 Gastric lavage, if ingested. Studies have shown that timolol cannot be easily removed by hemodialysis.
2 Symptomatic bradycardia: Atropine sulphate, 0.25 to 2mg 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 may be considered.
3 Hypotension: A sympathomimetic pressor agent such as dopamine, dobutamine or noradrenaline should be used. In refractory cases, the use of glucagon has been reported to be useful.
4 Bronchopasm: Isoprenaline hydrochloride should be used. Additional 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 suggested. This may be followed, if necessary, by glucagon which has been reported to be useful.
6 Heart block (second or third degree): Isoprenaline hydrochloride or a pacemaker should be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: S01ED01 Ophthalmological beta-blocking agent

Timolol is a non-selective β-adrenergic blocker, which does not possess significant intrinsic sympathomimetic or local anaesthetic (membrane-stabilising) activity. When applied topically in the eye, it reduces both elevated and normal intraocular pressure by inhibiting the production of aqueous humour.

Unlike miotics, Timolol reduces intraocular pressure with little or no effect on pupil size or accommodation.

The onset of reduction in intraocular pressure following ocular administration of timolol can be detected within 30 minutes after a single dose The maximum effect usually occurs in one to three hours and significant lowering of intraocular pressure can be maintained for as long as 24 hours following a single dose.

If systemically absorbed, as is possible, Timolol maleate is capable of producing beta-blockade elsewhere in the body with consequent systemic effects (increased airway resistance, bradycardia, hypotension etc.)

5.2 Pharmacokinetic properties

Topical instillation of 50µl of a 0.5% solution of timolol to the rabbit eye resulted in rapid appearance of timolol in the aqueous humour and to a much lesser degree in the plasma. The concentration in the aqueous humour (mean of 2.47µg/ml) peaked 30 minutes after instillation. The plasma concentration (0.188 µg/ml) also peaked at this time.

Following topical instillation in humans, the timolol concentration in aqueous humour was 8-100 ng/ml within the first hour while the mean plasma concentration was approximately 1 ng/ml within the first few hours (compared with plasma concentrations of 5-50 ng/ml seen with therapeutic doses of oral timolol).

5.3 Preclinical safety data

Acute Toxicity Studies: Data have been reported in a number of animal species. Oral LD_{50} in the mouse and rat are 1137 mg/kg and 1028 mg/kg respectively. Subcutaneous LD_{50} in the mouse and rat are 300 mg/kg and 381 mg/kg respectively.

Chronic Toxicity Studies: No adverse ocular effects were observed with ophthalmic topical administration of timolol in rabbits and dogs in studies lasting one and two years respectively. In studies with oral administration in high doses in dogs and rats,

bradycardia and weight increase in the heart, kidneys and liver were observed adverse effects.

Carcinogenicity: In a life-time study in mice, timolol increased the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice when administered orally at doses of 500mg/kg per day, but not at 5 or 50 mg/kg per day. In a 2 year study in rats, oral timolol increased the incidence of adrenal pheochromocytomas in male rats at 300 mg/kg per day but not at 25 or 100 mg/kg per day.

Mutagenicity: Timolol was not shown to be mutagenic when tested in vivo (mouse) in the micronucleus test and cytogenetic assay (at doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 0.1 mg per ml).

Reproduction and fertility: Reproduction and fertility studies in rats have not shown that timolol causes any adverse effects on male or female fertility when administered orally at doses of up to 125 times the maximum recommended human oral dose of 30mg. Studies in rats have shown that timolol at doses of up to 50mg/kg/day (50 times the maximum recommended human oral dose) caused delayed foetal ossification; however there were no adverse effects on post-natal development of offspring. Teratogenic studies in mice and rabbits have not shown that timolol at doses of up to 50 mg/kg/day causes foetal malformations. In mice, timolol at doses of 1000 mg/kg/day (1000 times the maximum recommended human oral dose) was maternotoxic and resulted in an increased incidence of foetal resorptions.

In rabbits, timolol at 100 mg/kg/day (100 times the maximum recommended human oral dose) increased incidence of foetal resorptions but not maternotoxicity.

Timolol maleate 0.25% eye drops have not been adequately studied in human pregnancy. Although timolol eye drops may be absorbed systemically, daily treatment with Timolol Eye Drops 0.25% (1 drop, twice daily in both eyes) will not exceed 0.4mgs timolol compared with the oral therapeutic dose of 20-60 mgs/day. However as a precautionary measure, it is recommended that timolol should not be used in pregnancy, unless the potential benefit to the pregnant woman exceeds the potential risk to the foetus.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Disodium edetate
Disodium phosphate dodecahydrate
Sodium dihydrogen phosphate dihydrate
Sodium chloride
Water for injection

6.2 Incompatibilities

Benzalkonium chloride may be deposited in soft contact lenses. These lenses should therefore be removed before instillation of the eye drops and not reinserted earlier than 15 minutes after use.

6.3 Shelf life

Unopened: 24 months
Opened: 28 days

6.4 Special precautions for storage

Do not store above 25^{o}C
To avoid contamination do not touch dropper tip to any surface.

6.5 Nature and contents of container

Low density polyethylene bottle with polystyrene spiked cap containing 5ml of solution.

6.6 Special precautions for disposal

None stated

7 MARKETING AUTHORISATION HOLDER

The Swiss Group Ltd
2nd Floor Manfield House
1 Southampton St
London WC2R 0LR
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 23097/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/07/2006

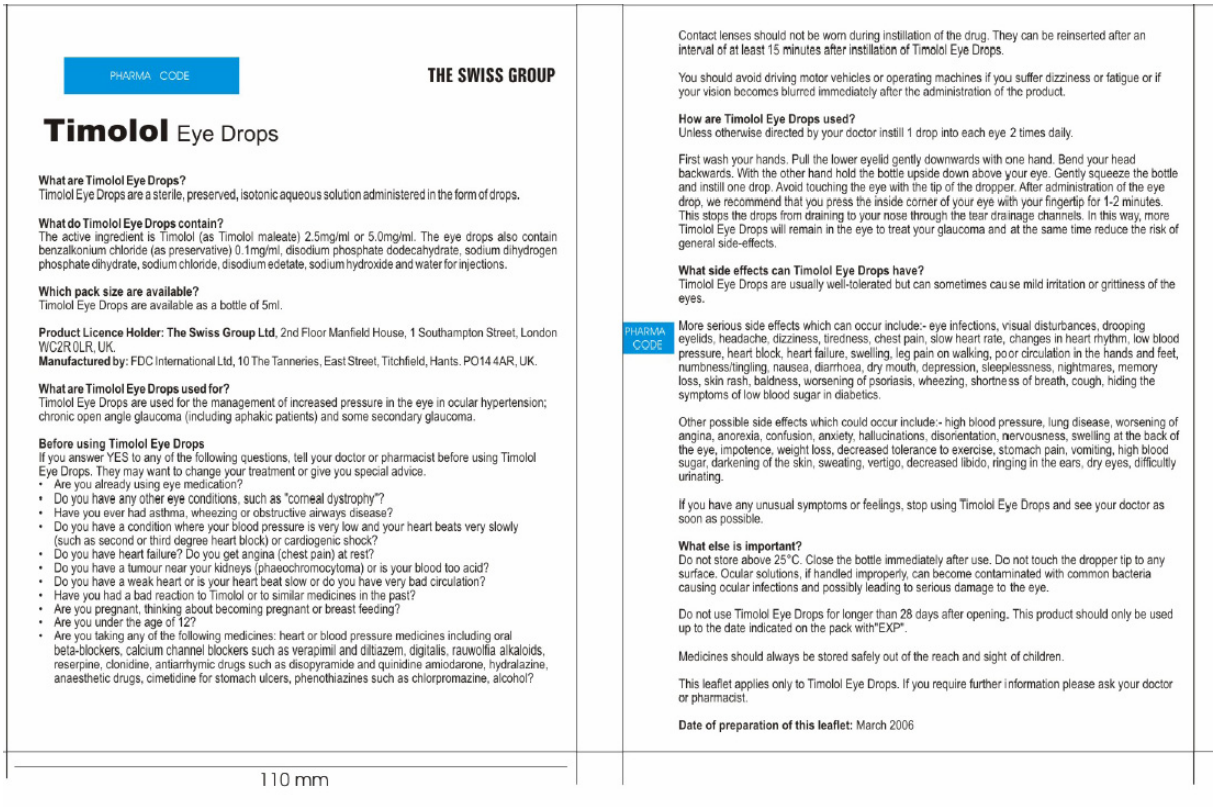
10 DATE OF REVISION OF THE TEXT

17/07/2006

Patient Information Leaflet

TIMOLOL 0.25%w/v EYE DROPS
PL 23097/0001

TIMOLOL 0.5%w/v EYE DROPS
PL 23097/0002



PHARMA CODE

THE SWISS GROUP

Timolol Eye Drops

What are Timolol Eye Drops?
Timolol Eye Drops are a sterile, preserved, isotonic aqueous solution administered in the form of drops.

What do Timolol Eye Drops contain?
The active ingredient is Timolol (as Timolol maleate) 2.5mg/ml or 5.0mg/ml. The eye drops also contain benzalkonium chloride (as preservative) 0.1mg/ml, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, disodium edetate, sodium hydroxide and water for injections.

Which pack size are available?
Timolol Eye Drops are available as a bottle of 5ml.

Product Licence Holder: The Swiss Group Ltd, 2nd Floor Manfield House, 1 Southampton Street, London WC2R 0LR, UK.
Manufactured by: FDC International Ltd, 10 The Tanneries, East Street, Titchfield, Hants. PO14 4AR, UK.

What are Timolol Eye Drops used for?
Timolol Eye Drops are used for the management of increased pressure in the eye in ocular hypertension; chronic open angle glaucoma (including aphakic patients) and some secondary glaucoma.

Before using Timolol Eye Drops
If you answer YES to any of the following questions, tell your doctor or pharmacist before using Timolol Eye Drops. They may want to change your treatment or give you special advice.

- Are you already using eye medication?
- Do you have any other eye conditions, such as "corneal dystrophy"?
- Have you ever had asthma, wheezing or obstructive airways disease?
- Do you have a condition where your blood pressure is very low and your heart beats very slowly (such as second or third degree heart block) or cardiogenic shock?
- Do you have heart failure? Do you get angina (chest pain) at rest?
- Do you have a tumour near your kidneys (phaeochromocytoma) or is your blood too acid?
- Do you have a weak heart or is your heart beat slow or do you have very bad circulation?
- Have you had a bad reaction to Timolol or to similar medicines in the past?
- Are you pregnant, thinking about becoming pregnant or breast feeding?
- Are you under the age of 12?
- Are you taking any of the following medicines: heart or blood pressure medicines including oral beta-blockers, calcium channel blockers such as verapimil and diltiazem, digitalis, rauwolfia alkaloids, reserpine, clonidine, antiarrhymic drugs such as disopyramide and quinidine amiodarone, hydralazine, anaesthetic drugs, cimetidine for stomach ulcers, phenothiazines such as chlorpromazine, alcohol?

110 mm

Contact lenses should not be worn during instillation of the drug. They can be reinserted after an interval of at least 15 minutes after instillation of Timolol Eye Drops.

You should avoid driving motor vehicles or operating machines if you suffer dizziness or fatigue or if your vision becomes blurred immediately after the administration of the product.

How are Timolol Eye Drops used?
Unless otherwise directed by your doctor instill 1 drop into each eye 2 times daily.

First wash your hands. Pull the lower eyelid gently downwards with one hand. Bend your head backwards. With the other hand hold the bottle upside down above your eye. Gently squeeze the bottle and instill one drop. Avoid touching the eye with the tip of the dropper. After administration of the eye drop, we recommend that you press the inside corner of your eye with your fingertip for 1-2 minutes. This stops the drops from draining to your nose through the tear drainage channels. In this way, more Timolol Eye Drops will remain in the eye to treat your glaucoma and at the same time reduce the risk of general side-effects.

What side effects can Timolol Eye Drops have?
Timolol Eye Drops are usually well-tolerated but can sometimes cause mild irritation or grittiness of the eyes.

PHARMA CODE

More serious side effects which can occur include:- eye infections, visual disturbances, drooping eyelids, headache, dizziness, tiredness, chest pain, slow heart rate, changes in heart rhythm, low blood pressure, heart block, heart failure, swelling, leg pain on walking, poor circulation in the hands and feet, numbness/tingling, nausea, diarrhoea, dry mouth, depression, sleeplessness, nightmares, memory loss, skin rash, baldness, worsening of psoriasis, wheezing, shortness of breath, cough, hiding the symptoms of low blood sugar in diabetics.

Other possible side effects which could occur include:- high blood pressure, lung disease, worsening of angina, anorexia, confusion, anxiety, hallucinations, disorientation, nervousness, swelling at the back of the eye, impotence, weight loss, decreased tolerance to exercise, stomach pain, vomiting, high blood sugar, darkening of the skin, sweating, vertigo, decreased libido, ringing in the ears, dry eyes, difficultly urinating.

If you have any unusual symptoms or feelings, stop using Timolol Eye Drops and see your doctor as soon as possible.

What else is important?
Do not store above 25°C. Close the bottle immediately after use. Do not touch the dropper tip to any surface. Ocular solutions, if handled improperly, can become contaminated with common bacteria causing ocular infections and possibly leading to serious damage to the eye.

Do not use Timolol Eye Drops for longer than 28 days after opening. This product should only be used up to the date indicated on the pack with "EXP".

Medicines should always be stored safely out of the reach and sight of children.

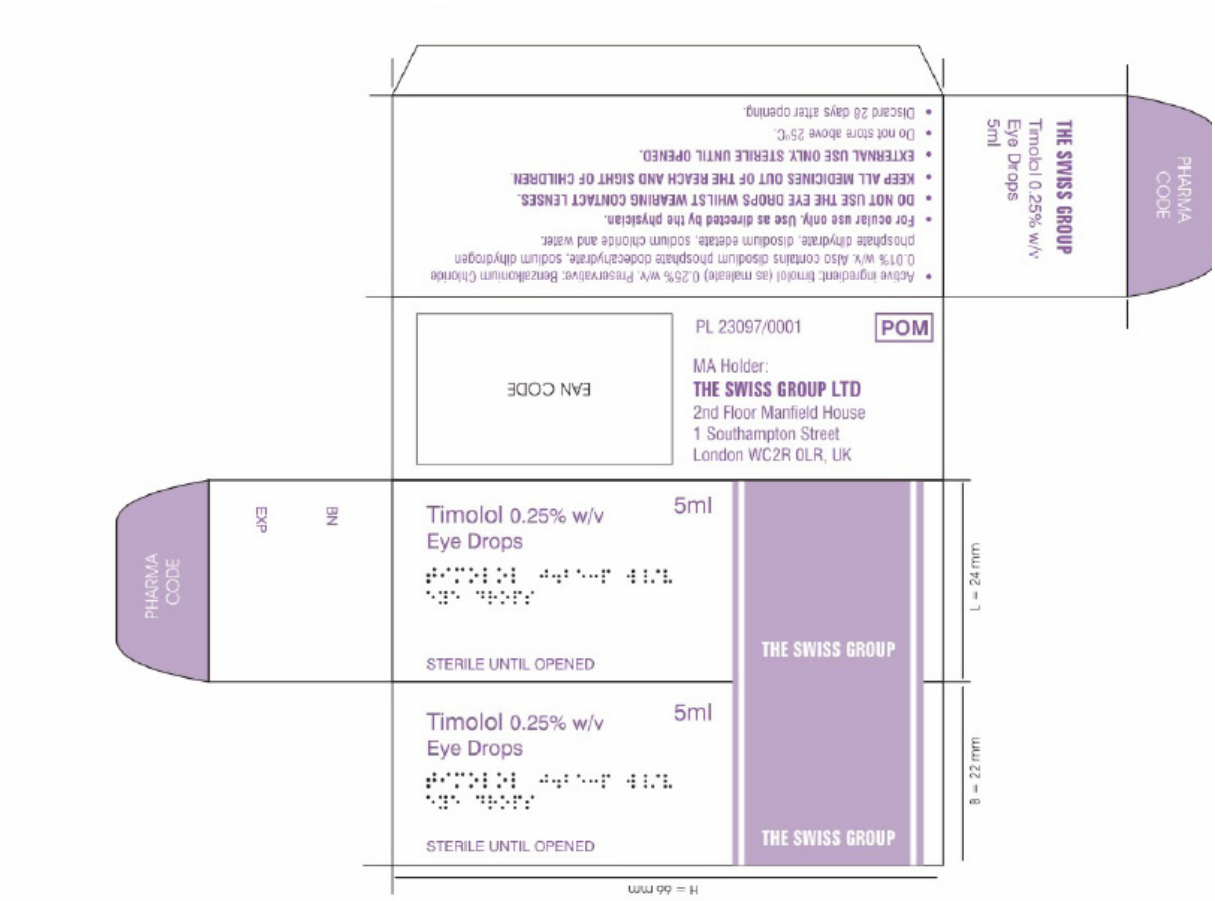
This leaflet applies only to Timolol Eye Drops. If you require further information please ask your doctor or pharmacist.

Date of preparation of this leaflet: March 2006

Labelling

TIMOLOL 0.25%w/v EYE DROPS
PL 23097/0001

TIMOLOL 0.5%w/v EYE DROPS
PL 23097/0002



TIMOLOL 0.25%w/v EYE DROPS
PL 23097/0001

TIMOLOL 0.5%w/v EYE DROPS
PL 23097/0002