Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bitifrin 0.3 mg/ml + 5 mg/ml eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 0.3 mg of bimatoprost and 5 mg of timolol (as 6.83 mg of timolol maleate).
Each 5 ml bottle contains 3 ml of solution.
Each 11 ml bottle contains 9 ml of solution

Excipient with known effect:
Each ml of solution contains about 0.95 mg phosphates.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution

Transparent, colourless, solution

pH: 6.8 to 7.6
osmolality: 270 to 320 mosmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

4.2 Posology and method of administration

Posology

Recommended dosage in adults (including older people)
The recommended dose is one drop of Bitifrin in the affected eye(s) once daily, administered either in the morning or in the evening. It should be administered at the same time each day.

Existing literature data for bimatoprost/timolol suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing (see section 5.1).

If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.

Renal and hepatic impairment
Bitifrin has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.

Paediatric population
The safety and efficacy of Bitifrin in children aged less than 18 years has not been established. No data are available.

Method of administration

For ocular use only.

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.

If more than one topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart. Eye ointments should be administered last.

4.3 Contraindications

- Hypersensitivity to the active substances 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.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic medicinal products, the active substances (bimatoprost/timolol) in Bitifrin may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions (ADRs) as seen with systemic beta-blockers may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders
Patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and receiving hypotension therapy with beta-blockers should be critically assessed and 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 the negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

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

Respiratory disorders
Respiratory reactions, including death due to bronchospasm in patients with asthma, have been reported following administration of some ophthalmic beta-blockers.

Bitifrin should be used with caution in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Endocrine disorders
Beta-adrenergic blocking medicinal products should be administered with caution in patients subject to spontaneous hypoglycaemia or in patients with labile diabetes as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

Beta-blockers may also mask the signs of hyperthyroidism.

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

Other beta-blocking agents
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to 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 a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

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

Surgical anaesthesia
Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Hepatic
In patients with a history of mild liver disease or abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline, bimatoprost eye drops had no adverse reactions on liver function over 24 months. There are no known adverse reactions of ocular timolol on liver function.

Ocular
Before treatment is initiated, patients should be informed of the possibility of prostaglandin analogue periorbitopathy (PAP) and increased brown iris pigmentation since these have been observed during treatment with bimatoprost and bimatoprost/timolol. Increased iris pigmentation is likely to be permanent, and may lead to impaired field of vision and differences in appearance between the eyes if only one eye is treated (see section 4.8).

Macular oedema, including cystoid macular oedema has been reported with bimatoprost/timolol fixed combination. Therefore, Bitifrin should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).
Bitifrin should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

Skin
There is a potential for hair growth to occur in areas where Bitifrin solution comes repeatedly in contact with the skin surface. Thus, it is important to apply Bitifrin as instructed and avoid it running onto the cheek or other skin areas.

Other conditions
Bimatoprost/timolol has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure, congenital or narrow-angle glaucoma.

In studies of bimatoprost 0.3 mg/ml in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than 1 dose of bimatoprost daily may decrease the IOP-lowering effect. Patients using Bitifrin with other prostaglandin analogues should be monitored for changes to their intraocular pressure.

Patients with a history of contact hypersensitivity to silver should not use this product as dispensed drops may contain traces of silver.

Bitifrin is preservative-free and has not been studied in patients wearing contact lenses. Contact lenses should be removed prior to application, with at least a 15-minute wait before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with the bimatoprost/timolol fixed combination.

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, guanethidine, beta-adrenergic blocking agents, parasympathomimetics, anti-arrhythmics (including amiodarone) and digitalis glycosides.

Potentiated systemic beta-blockade (e.g. decreased heart rate, 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of the bimatoprost/timolol fixed combination in pregnant women. Bitifrin should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Bimatoprost
No adequate clinical data in exposed pregnancies are available. Animal studies have shown reproductive toxicity at high maternotoxic doses (see section 5.3).

Timolol
Epidemiological studies have not revealed malformative effects but shown a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If bimatoprost/timolol is administered until delivery, the neonate should be carefully monitored during the first days of life. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice (see section 5.3).

Breastfeeding
Timolol
Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

Bimatoprost
It is not known if bimatoprost is excreted in human breast milk but it is excreted in the milk of the lactating rat. Bitifrin should not be used by breast-feeding women.

Fertility
There are no data on the effects of Bitifrin on human fertility.

4.7 Effects on ability to drive and use machines

Bitifrin has negligible influence on the ability to drive and use machines. As with any topical ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Bimatoprost/timolol

Summary of the safety profile
The adverse reactions reported in the clinical study using bimatoprost/timolol single-dose were limited to those earlier reported for either the bimatoprost/timolol multi-dose formulation with preservative or for the single active substances bimatoprost or timolol. No new adverse reactions specific for bimatoprost/timolol single-dose preservative-free formulation have been observed in clinical studies.

The majority of adverse reactions reported with bimatoprost/timolol single-dose preservative-free formulation were ocular, mild in severity and none were serious. Based on a 12-week study the most commonly reported adverse reaction was conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in approximately 21% of patients and led to discontinuation in 1.4% of patients.

Tabulated list of adverse reactions
Table 1 presents the adverse reactions that were reported during clinical studies of both bimatoprost/timolol single-dose preservative-free formulation and bimatoprost/timolol multi-dose formulations with preservative (within each frequency grouping, adverse reactions are presented in order of decreasing seriousness) or in the post-marketing period.

The frequency of possible adverse reactions listed below is defined using the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Not known	Frequency cannot be estimated from available data

Table 1

System Organ Class	Frequency	Adverse reaction
Immune system disorders	Not known	hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy
Psychiatric disorders	Not known	insomnia[2], nightmare[2]
Nervous system disorders	Common	headache
	Not known	dysgeusia[2], dizziness[2]
Eye disorders	Very common	conjunctival hyperaemia, prostaglandin analogue periorbitopathy
	Common	punctuate keratitis, corneal erosion[2], burning sensation[2], conjunctival irritation[1], eye pruritus, stinging sensation in the eye[2], foreign body sensation, dry eye, erythema of eyelid, eye pain, photophobia, eye discharge[2], visual disturbance[2], eyelid pruritus, visual acuity worsened[2], blepharitis[2], eyelid oedema, eye irritation, lacrimation increased, growth of eyelashes
	Uncommon	iritis[2], conjunctival oedema[2], eyelid pain[2], abnormal sensation in the eye[1], asthenopia, trichiasis[2], iris hyperpigmentation[2], eyelid retraction[2], eyelash discolouration (darkening)[1]
	Not known	cystoid macular oedema[2], eye swelling, vision blurred[2], ocular discomfort
Cardiac disorders	Not known	bradycardia
Vascular disorders	Not known	hypertension
Respiratory, thoracic and mediastinal disorders	Common	rhinitis[2]
	Uncommon	dyspnoea
	Not known	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)[2], asthma
Skin and subcutaneous tissue disorders	Common	blepharal pigmentation[2], hirsutism[2], skin hyperpigmentation (periocular)
	Not known	alopecia[2], skin discolouration (periocular)
General disorders and administration site conditions	Not known	fatigue

[1]adverse reactions only observed with bimatoprost/timolol preservative-free formulation
[2]adverse reactions only observed with bimatoprost/timolol formulation with preservative (benzalkonium chloride)

Description of selected adverse reactions

Prostaglandin analogue periorbitopathy (PAP)
Prostaglandin analogues including Bitifrin can induce periorbital lipodystrophic changes which can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involution of dermatochalasis and inferior scleral show. Changes are typically mild, can occur as early as one month after initiation of treatment with Bitifrin, and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discoloration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.

Iris hyperpigmentation
Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long-term effects of increased iris pigmentation are not known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the

entire iris or parts become more brownish. Neither naevi nor freckles of the iris appear to be affected by the treatment. After 12 months of treatment with bimatoprost/timolol fixed combination, the incidence of iris pigmentation was 0.2%. After 12 months of treatment with bimatoprost 0.3 mg/ml eye drops alone, the incidence was 1.5% and did not increase following 3 years of treatment.

Like other topically applied ophthalmic drugs, bimatoprost/timolol is absorbed into the systemic circulation. Absorption of timolol may cause similar undesirable effects as seen with systemic beta-blocking agents. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Additional adverse reactions that have been seen with either of the active substances (bimatoprost or timolol), and may potentially occur also with bimatoprost/timolol are listed below in Table 2:

Table 2

System Organ Class	**Adverse reaction**
Immune system disorders	systemic allergic reactions including anaphylaxis[1]
Metabolism and nutrition disorders	hypoglycaemia[1]
Psychiatric disorders	depression[1], memory loss[1], hallucination[1]
Nervous system disorders	syncope[1], cerebrovascular accident[1], increase in signs and symptoms of myasthenia gravis[1], paraesthesia[1], cerebral ischaemia[1]
Eye disorders	decreased corneal sensitivity[1], diplopia[1], ptosis[1], choroidal detachment following filtration surgery (see section 4.4)[1], keratitis[1], blepharospasm[2], retinal haemorrhage[2], uveitis[2]
Cardiac disorder	atrioventricular block[1], cardiac arrest[1], arrhythmia[1], cardiac failure[1], congestive heart failure[1], chest pain[1], palpitations[1], oedema[1]
Vascular disorders	hypotension[1], Raynaud's phenomenon[1], cold hands and feet[1]
Respiratory, thoracic and mediastinal disorders	asthma exacerbation[2], COPD exacerbation[2], cough[1]
Gastrointestinal disorders	nausea[1,2], diarrhoea[1], dyspepsia[1], dry mouth[1], abdominal pain[1], vomiting[1]
Skin and subcutaneous tissue disorders	psoriasiform rash[1] or exacerbation of psoriasis[1], skin rash[1]
Musculoskeletal and connective tissue disorders	myalgia[1]
Reproductive system and breast disorders	sexual dysfunction[1], decreased libido[1]
General disorders and administration site conditions	asthenia[1,2]
Investigations	liver function tests (LFT) abnormal[2]

[1] adverse reactions observed with timolol
[2] adverse reactions observed with bimatoprost

Adverse reactions reported in phosphate containing eye drops
Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly 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
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

A topical overdose with bimatoprost/timolol is not likely to occur or to be associated with toxicity.

Bimatoprost
If bimatoprost/timolol is accidentally ingested, the following information may be useful: in two-week oral mice and rats studies, doses of bimatoprost up to 100 mg/kg/day did not produce any toxicity; this corresponds to a human equivalent dose of 8.1 and 16.2 mg/kg, respectively. This dose expressed as mg/m2 is at least 70 -times higher than the accidental dose of one bottle of Bitifrin in 10 kg child.

Timolol
Symptoms of systemic timolol overdose include: bradycardia, hypotension, bronchospasm, headache, dizziness, shortness of breath, and cardiac arrest. A study of patients with renal failure showed that timolol did not dialyse readily.

If overdose occurs treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ophthalmological, beta-blocking agents, ATC code: S01ED51

Mechanism of action
Bitifrin consists of two active substances: bimatoprost and timolol. These two components decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone. Bimatoprost/timolol has a rapid onset of action.

Bimatoprost is a potent ocular hypotensive active substance. It is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) that does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. The mechanism of action by which bimatoprost reduces intraocular pressure in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a $beta_1$ and $beta_2$ non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

Clinical effects
A 12-week (double-masked, randomized, parallel group) clinical study compared the efficacy and safety of bimatoprost/timolol in single-dose preservative-free formulation with bimatoprost/timolol multi-dose formulation with preservative (benzalkonium chloride) in patients with glaucoma or ocular hypertension. Bimatoprost/timolol single dose preservative-free formulation achieved noninferior IOP-lowering efficacy to bimatoprost/timolol multi-dose formulation with preservative (benzalkonium chloride): the upper limit of the 95% CI of the between-treatment difference was within the pre-defined 1.5 mm Hg margin at each timepoint evaluated (hours 0, 2, and 8) at week 12 (for the primary analysis), and also at weeks 2 and 6, for mean worse eye IOP change from baseline (worse eye IOP refers to the eye with the higher mean diurnal IOP at baseline). In fact, the upper limit of the 95% CI did not exceed 0.14 mm Hg at week 12.

Both treatment groups showed statistically and clinically significant mean decreases from baseline in worse eye IOP at all follow up timepoints throughout the study ($p < 0.001$). Mean changes from baseline worse eye IOP ranged from -9.16 to -7.98 mm Hg for bimatoprost/timolol single-dose preservative-free formulation group, and from -9.03 to -7.72 mm Hg for the bimatoprost/timolol multi-dose formulation with preservative group across the 12-week study.

Bimatoprost/timolol in single-dose preservative-free formulation also achieved equivalent IOP-lowering efficacy to bimatoprost/timolol multi-dose formulation with preservative in average eye and worse eye IOP at each follow-up timepoint at weeks 2, 6 and 12.

Based on studies of bimatoprost/timolol multi-dose formulation with preservative, the IOP-lowering effect of bimatoprost/timolol is non-inferior to that achieved by adjunctive therapy of bimatoprost (once daily) and timolol (twice daily).

Existing literature data for bimatoprost/timolol multi-dose formulation with preservative suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing.

Paediatric population
The safety and efficacy of bimatoprost/timolol in children aged less than 18 years has not been established.

5.2 Pharmacokinetic properties

Bimatoprost/timolol medicinal product
Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to bimatoprost/timolol multi-dose formulation with preservative treatment in healthy subjects. Systemic absorption of the individual components was minimal and not affected by co-administration in a single formulation.

In two 12-month studies of bimatoprost/timolol multi-dose formulation with preservative in which systemic absorption was measured, no accumulation was observed of either of the individual components.

Bimatoprost
Bimatoprost penetrates the human cornea and sclera well *in vitro*. After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over time. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/ml) within 1.5 hours after dosing. Mean C_{max} and AUC $_{0\text{-}24hrs}$ values were similar on days 7 and 14 at approximately 0.08 ng/ml and 0.09 ng•hr/ml respectively, indicating that a steady drug concentration was reached during the first week of ocular dosing.

Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady-state was 0.67 1/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88%.

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Bimatoprost is eliminated primarily by renal excretion, up to 67% of an intravenous dose administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes; the total blood clearance was 1.5 1/hr/kg.

Characteristics in older people
After twice daily dosing of bimatoprost 0.3 mg/ml, the mean AUC $_{0\text{-}24hrs}$ value of 0.0634 ng•hr/ml bimatoprost in the elderly (subjects 65 years or older) were significantly higher than 0.0218 ng•hr/ml in young healthy adults. However, this finding is not clinically relevant as systemic exposure for both elderly and young subjects remained very low from ocular dosing. There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients.

Timolol
After ocular administration of a 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/ml in the aqueous humour at one hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 4 to 6 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma.

5.3 Preclinical safety data

Bimatoprost/timolol medicinal product
Repeated dose ocular toxicity studies on bimatoprost/timolol multi-dose formulation with preservative showed no special hazard for humans. The ocular and systemic safety profile of the individual components is well established.

Bimatoprost
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential. Studies in rodents produced species-specific abortion at systemic exposure levels 33- to 97-times that achieved in humans after ocular administration.

Monkeys administered ocular bimatoprost concentrations of ≥0.03% daily for 1 year had an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. The increased iris pigmentation appears to be caused by increased stimulation of melanin production in melanocytes and not by an increase in melanocyte number. No functional or microscopic changes related to the periocular effects have been observed, and the mechanism of action for the periocular changes is unknown.

Timolol

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dodecahydrate
Citric acid monohydrate
Sodium chloride
Sodium hydroxide or hydrochloric acid, diluted (for pH-adjustment)
Water purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
Discard 90 days after the first opening of the bottle.

For storage conditions of the product after the first opening of the bottle, see section 6.4.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
After first opening of the bottle, store below 25°C.

6.5 Nature and contents of container

White LDPE bottle (containing 3 ml and 9 ml solution, respectively) with multidose HDPE dropper applicator and tamper-proof HDPE screw-cap and the carton box.

Pack sizes:
1 bottle of 3 ml
1 bottle of 9 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Farmaprojects S.A.
Calle Provenca 392 6 Planta
Barcelona
08025
Spain

8 MARKETING AUTHORISATION NUMBER

PA1391/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd September 2022

10 DATE OF REVISION OF THE TEXT