Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

TAPTIQOM 15 micrograms/ml + 5 mg/ml eye drops, solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 15 micrograms tafluprost and 5 mg timolol (as timolol maleate).

One drop (about 0.03 ml) contains about 0.45 micrograms of tafluprost and 0.15 mg of timolol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution (eye drops).

A clear, colourless solution, practically free from visible particles with a pH of 6.0-6.7 and an osmolality of 290-370 mOsm/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 monotherapy with beta-blockers or prostaglandin analogues.

4.2 Posology and method of administration

Posology
Recommended therapy is one eye drop in the conjunctival sac of the affected eye(s) once daily.

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.

TAPTIQOM is a preservative free sterile solution packaged in a multi-dose container.

Paediatric population
The safety and efficacy of TAPTIQOM in children and adolescents below the age of 18 years have not been established. No data are available.

TAPTIQOM is not recommended for use in children and adolescents below the age of 18 years.

Use in elderly
No dosage alteration in elderly patients is necessary.

Use in renal/hepatic impairment
Tafluprost and timolol eye drops have not been studied in patients with renal/hepatic impairment and TAPTIQOM should therefore be used with caution in such patients.

Method of administration
Ocular use
Patients should be informed of the correct handling of the bottle. When using for the first time, before delivering a drop to the eye, the patient should first of all practise using the bottle by squeezing it slowly to deliver one drop away from the eye. The patient should practice until being confident to deliver one drop at a time.

Patients should be instructed to avoid allowing the container to come into contact with the eye or surrounding structures as this could cause injury to the eye.

Patients should be instructed not touch their eyelids, surrounding areas or any other surfaces with the applicator tip of the bottle. The residual liquid remaining at the dropper tip after application of the eye drops should immediately be removed by shaking the bottle once downwards. The dropper tip should not be touched or wiped.

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.

To reduce the risk of darkening of the eyelid skin the patients should wipe off any excess solution from the skin.

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 of local activity.

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

Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.

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, including 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

Systemic effects:
Like other topically applied ophthalmic agents, tafluprost and timolol are absorbed systemically. Due to the beta-adrenergic component timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic adverse reactions after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

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.

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

Hypoglycemia/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. Abrupt withdrawal of beta-blocker therapy may precipitate a worsening of symptoms.

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 (a component of TAPTIQOM) 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 b-adrenergic blocking agents is not recommended.

Angle-closure glaucoma:
In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol has little or no effect on the pupil. When timolol is used to reduce elevated intraocular pressure in angle-closure glaucoma it should be used with a miotic and not alone.

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 doses 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.

Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation which are related to tafluprost therapy. Some of these changes may be permanent, and may lead to differences in appearance between the eyes when only one eye is treated.

The change in iris pigmentation occurs slowly and may not be noticeable for several months. The change in eye colour has predominantly been seen in patients with mixed coloured irises, e.g. blue-brown, grey-brown, yellow-brown and green-brown. The risk of lifelong heterochromia between the eyes in unilateral cases is obvious.

There is a potential for hair growth to occur in areas where tafluprost solution comes repeatedly in contact with the skin surface.

There is no experience with tafluprost in neovascular, angle-closure, narrow-angle or congenital glaucoma. There is only limited experience with tafluprost in aphakic patients and in pigmentary or pseudoexfoliative glaucoma.

Caution is recommended when using tafluprost in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema or iritis/uveitis.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed.

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, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

Oral b-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

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 or limited amount of data from the use of TAPTIQOM in pregnant women.

Women of childbearing potential have to use effective contraception during TAPTIQOM treatment.

TAPTIQOM should not be used during pregnancy unless clearly necessary (in case no other treatment options are available).

Tafluprost:
There are no adequate data for the use of tafluprost in pregnant women. Tafluprost can have harmful pharmacologic effects on pregnancy and/or the fetus/newborn child. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

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

It is unknown whether tafluprost and/or its metabolites are excreted in human milk. Available toxicological data in animals have shown excretion of tafluprost and/or its metabolites in milk (for details see section 5.3). However, at therapeutic doses of tafluprost in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms in the infant.

As a precautionary measure lactation is not recommended if treatment with TAPTIQOM is required.

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

4.7 Effects on ability to drive and use machines

No studies on the effects of TAPTIQOM on the ability to drive and use machines have been performed. If adverse reactions such as transient blurred vision occurs at instillation, the patient should not drive or operate machinery until the patient feels well and has clear vision.

4.8 Undesirable effects

In clinical studies, over 484 patients have been treated with Taptiqom in single-dose container. The most frequently reported treatment-related adverse event was conjunctival/ocular hyperaemia. It occurred in approximately 7% of the patients participating in the clinical studies in Europe, was mild in most cases, and was associated with discontinuation of treatment in 1.2% of patients.

The adverse reactions reported in the clinical studies using Taptiqom in single-dose container were limited to those earlier reported for either of the single active substances tafluprost or timolol. No new adverse reactions specific for Taptiqom in single-dose container were observed in the clinical studies. The majority of adverse reactions reported were ocular, mild or moderate in severity and none were serious.

Like other topically applied ophthalmic agents, tafluprost and timolol are absorbed systemically. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic adverse reactions after topical

ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

The following adverse reactions have been reported with Taptiqom in single-dose container during clinical trials (within each frequency grouping, adverse reactions are presented in order of decreasing frequency).

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 the available data

Taptiqom(Tafluprost/timolol combination)

System Organ Class	Frequency	Adverse Reactions
Nervous system disorders	Uncommon	Headache.
Eye disorders	Common	Conjunctival/ocular hyperaemia, eye pruritus, eye pain, change of eyelashes (increased length, thickness and number of lashes), eyelash discolouration, eye irritation, foreign body sensation in eyes, blurred vision, photophobia.
	Uncommon	Abnormal sensation in eye, dry eye, ocular discomfort, conjunctivitis, erythema of eyelid, eye allergy, eyelid oedema, superficial punctate keratitis, lacrimation increased, anterior chamber inflammation, asthenopia, blepharitis.

Additional adverse reactions that have been seen with either of the active substances (tafluprost or timolol), and may potentially occur also with Taptiqom are listed below:

Tafluprost

System Organ Class	Adverse Reactions
Eye disorders	Reduced visual acuity, increased iris pigmentation, blepharal pigmentation, conjunctival oedema, eye discharge, anterior chamber cell, anterior chamber flare, allergic conjunctivitis, conjunctival pigmentation, conjunctival follicles, deepening of eye lid sulcus, iritis/uveitis, macular oedema/cystoid macular oedema.
Skin and subcutaneous tissue disorders	Hypertrichosis of eyelid.
Respiratory disorders	Exacerbation of asthma, dyspnea.

Timolol

System Organ Class	Adverse Reactions
Immune system disorders	Signs and symptoms of allergic reactions including angioedema, urticaria, localized and generalized rash, anaphylaxis, pruritus.
Metabolism and nutrition disorders	Hypoglycaemia.
Psychiatric disorders	Depression, insomnia, nightmares, memory loss, nervousness, hallucination.
Nervous system disorders	Dizziness, syncope, paraesthesia, increase in signs and symptoms of myasthenia gravis, cerebrovascular accident, cerebral ischaemia.
Eye disorders	Keratitis, decreased corneal sensitivity, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), ptosis, diplopia, choroidal detachment following filtration surgery (see Special warning and precautions for use 4.4), tearing, corneal erosion.
Ear and labyrinth disorders	Tinnitus.
Cardiac disorders	Bradycardia, chest pain, palpitation, oedema, arrhythmia, congestive heart failure, cardiac arrest, heart block, atrioventricular block, cardiac failure.
Vascular disorders	Hypotension, claudication, Raynaud's phenomenon, cold hands and feet.
Respiratory, thoracic, and mediastinal disorders	Dyspnoea, bronchospasm (predominantly in patients with

	pre-existing bronchospastic disease), respiratory failure, cough.
Gastrointestinal disorders	Nausea, dyspepsia, diarrhoea, dry mouth, dysgeusia, abdominal pain, vomiting.
Skin and subcutaneous tissue disorders	Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.
Musculoskeletal and connective tissue disorders	Systemic lupus erythematosus, myalgia, arthropathy.
Reproductive system and breast disorders	Peyronie's disease, decreased libido, sexual dysfunction.
General disorders and administration site conditions	Asthenia/fatigue, thirst.

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 the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

A topical overdose with tafluprost is not likely to occur or to be associated with toxicity.

There have been reports of inadvertent overdose with timolol resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also section 4.8).

If overdose with Taptiqom occurs, treatment should be symptomatic and supportive. Timolol does not dialyse readily.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, beta blocking agents, ATC code: S01ED51

Mechanism of action
TAPTIQOM is a fixed combination of two active substances tafluprost and timolol. These two active substances lower intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone.

Tafluprost is a fluorinated analogue of prostaglandin $F_{2\alpha}$. Tafluprost acid, the biologically active metabolite of tafluprost, is a highly potent and selective agonist of the human prostanoid FP receptor. Pharmacodynamic studies in monkeys indicate that tafluprost reduces intraocular pressure by increasing the uveoscleral outflow of aqueous humour.

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

Clinical efficacy
In a 6-month study (n=400) in patients with open-angle glaucoma or ocular hypertension and mean untreated IOPs between 24-26 mmHg, the IOP lowering effect of Taptiqom in single-dose container (once daily in the morning) was compared to concomitant administration of 0.0015% tafluprost (once daily in the morning) and 0.5% timolol (twice daily). Taptiqom was non-inferior to the effect of concomitantly used 0.0015% tafluprost and 0.5% timolol at all time points and visits with the generally used non-inferiority margin of 1.5 mmHg. The mean diurnal IOP decrease from baseline was 8 mmHg in both arms at the primary endpoint of 6 months (decreases ranging between 7 to 9 mmHg in both arms at the different time points during the day over the study visits).

Another 6-month study (n=564) compared Taptiqom in single-dose container with the respective monotherapies in patients with open-angle glaucoma or ocular hypertension and mean untreated IOPs between 26-27 mmHg. Patients insufficiently

controlled either with 0.0015% tafluprost (IOP 20 mmHg or greater on treatment) or 0.5% timolol (IOP 22 mmHg or greater on treatment) were randomized to be treated with Taptiqom in single-dose container or the same monotherapy. The mean diurnal IOP reduction of Taptiqom was statistically superior to that of tafluprost given once daily in the morning or timolol given twice daily, at visits 6 weeks, 3 months (primary efficacy endpoint) and 6 months. The mean diurnal IOP decrease from baseline of Taptiqom at 3 months was 9 mmHg, in comparison to 7 mmHg observed for both monotherapies. IOP decreases with Taptiqom at the different time points during the day over the visits ranged between 8 to 9 mmHg in the tafluprost monotherapy comparison group and between 7 to 9 mmHg in the timolol monotherapy comparison group.

Combined data from Taptiqom patients with high baseline IOP of 26 mmHg (mean diurnal) or above in these two pivotal studies (n=168) showed that the mean diurnal reduction in the IOP was 10 mmHg at the primary end point (3 or 6 months) ranging between 9 and 12 mmHg at the different time points during the day.

The European Medicines Agency has waived the obligation to submit the results of studies with Taptiqom (tafluprost/timolol combination) in all subsets of the paediatric population (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Plasma concentrations of tafluprost acid and timolol were investigated in healthy volunteers after single and repeated ocular dosing for eight days of Taptiqom (once daily), 0.0015% tafluprost (once daily) and 0.5% timolol (twice daily). Tafluprost acid plasma concentrations peaked at 10 minutes after dosing and declined below the lower limit of detection (10 pg/ml) before 30 minutes after Taptiqom dosing. Accumulation of tafluprost acid was negligible and the tafluprost acid mean $AUC_{0\text{-last}}$ (monotherapy: 4.45±2.57 pg·h/ml; Taptiqom: 3.60±3.70 pg·h/ml) and the mean C_{max} (monotherapy: 23.9±11.8 pg/ml; Taptiqom: 18.7±11.9 pg/ml) were both slightly lower with Taptiqom as compared to tafluprost monotherapy on Day 8. Timolol plasma concentrations peaked at median T_{max} values of 15 and 37.5 minutes after Taptiqom dosing on Days 1 and 8, respectively. The Day 8 timolol mean $AUC_{0\text{-last}}$ (monotherapy: 5750±2440 pg·h/ml; Taptiqom:4560±2980 pg·h/ml) and the mean C_{max} (monotherapy: 1100 ± 550 pg/ml; Taptiqom: 840 ± 520 pg/ml) were both somewhat lower with Taptiqom compared to timolol monotherapy. The lower plasma timolol exposure with Taptiqom appears to be due to once-daily dosing for Taptiqom versus twice daily dosing with timolol monotherapy.

Tafluprost and timolol are absorbed through the cornea. In rabbits, corneal penetration of tafluprost from Taptiqom was similar to that of tafluprost monopreparation after a single instillation while the penetration of timolol was slightly less from the Taptiqom compared to timolol monopreparation. For tafluprost acid, AUC_{4h} was 7.5 ng·h/ml following administration of Taptiqom and 7.7 ng·h/ml following administration of tafluprost monopreparation. For timolol, AUC_{4h} was 585 ng·h/ml and 737 ng·h/ml following administration of Taptiqom and timolol monopreparation, respectively. T_{max} for tafluprost acid was 60 minutes for both Taptiqom and tafluprost monopreparation, while for timolol T_{max} was 60 min for Taptiqom and 30 min for timolol monopreparation.

Distribution

Tafluprost

In monkeys, there was no specific distribution of radiolabelled tafluprost in the iris-ciliary body or choroid including retinal pigment epithelium, which suggested low affinity for melanin pigment. In a whole body autoradiography study in rats, the highest concentration of radioactivity was observed in the cornea followed by the eyelids, sclera and the iris. Outside the eye radioactivity was distributed to the lacrimal apparatus, palate, oesophagus and gastrointestinal tract, kidney, liver, gall bladder and urinary bladder. The binding of tafluprost acid to human serum albumin *in vitro* was 99% at 500 ng/ml tafluprost acid.

Timolol

The peak level of timolol-related radioactivity in the aqueous humor was reached after 30 minutes following a single application of ^{3}H-radiolabelled timolol (0.5% solution: 20 µl/eye) to both eyes in rabbits**.** Timolol is eliminated from the aqueous humor much faster than from the pigmented tissues iris and ciliary body.

Biotransformation

Tafluprost

The principal metabolic pathway of tafluprost in human, which was tested *in vitro*, is the hydrolysis to the pharmacologically active metabolite, tafluprost acid, which is further metabolized by glucuronidation or beta-oxidation. Products of beta-oxidation, 1,2-dinor and 1,2,3,4-tetranor tafluprost acids, which are pharmacologically inactive, may be glucuronidated or hydroxylated. Cytochrome P450 (CYP) enzyme system is not involved in the metabolism of tafluprost acid. Based on the study

in rabbit corneal tissue and with purified enzymes, the main esterase responsible for the ester hydrolysis to tafluprost acid is carboxyl esterase. Butylcholine esterase but not acetylcholine esterase may also contribute to the hydrolysis.

Timolol
Timolol is metabolized in the liver primarily by CYP2D6 enzyme into inactive metabolites, which are excreted primarily through the kidneys.

Elimination

Tafluprost
Following once daily administration of ^{3}H-tafluprost (0.005% ophthalmic solution; 5 µl/eye) for 21 days to both eyes in rats, approximately 87% of the total radioactive dose was recovered in the excreta. Percent of the total dose excreted in urine was approximately 27-38% and approximately 44-58% of the dose was excreted in the feces.

Timolol
Apparent elimination half-life from the human plasma is about 4 hours. Timolol is extensively metabolised in the liver and the metabolites are excreted in the urine in addition to 20% unchanged timolol following oral administration.

5.3 Preclinical safety data

Taptiqom
Non-clinical data reveal no special hazard for humans based on repeated dose toxicity study and ocular pharmacokinetic studies. The ocular and systemic safety profile of the individual components is well established.

Tafluprost
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, systemic repeated dose toxicity, genotoxicity and carcinogenic potential. As with other PGF2 agonists, repeated dose topical ocular administration of tafluprost to monkeys produced irreversible effects on iris pigmentation and reversible enlargement of the palpebral fissure.

Increased contraction of rat and rabbit uteri *in vitro* was observed at tafluprost acid concentrations that exceeded 4 to 40 times, respectively, the maximum plasma concentrations of tafluprost acid in humans. Uterotonic activity of tafluprost has not been tested in human uterus preparations.

Reproduction toxicity studies were performed in the rat and rabbit with intravenous administration. In rats, no adverse effects on fertility or early embryonic development were observed at systemic exposure over 12,000 times the maximum clinical exposure based on C_{max} or greater than 2,200 times based on AUC.

In conventional embryo-foetal development studies, tafluprost caused reductions in foetal body weights and increases in post-implantation losses. Tafluprost increased the incidence of skeletal abnormalities in rats as well as the incidence of skull, brain and spine malformations in rabbits. In the rabbit study, plasma levels of tafluprost and its metabolites were below the level of quantification.

In a pre- and postnatal development study in rats, increased mortality of newborns, decreased body weights and delayed pinna unfolding were observed in offspring at tafluprost doses greater than 20 times the clinical dose.

The experiments in rats with radiolabelled tafluprost showed that around 0.1% of the topically applied dose on eyes was transferred into milk. As the half-life of active metabolite (tafluprost acid) in plasma is very short (not detectable after 30 minutes in humans), most of the radioactivity probably represented metabolites with little, or no pharmacologic activity. Based on metabolism of tafluprost and natural prostaglandins, the oral bioavailability is expected to be very low.

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

Glycerol
Disodium phosphate dodecahydrate
Disodium edetate
Polysorbate 80
Hydrochloric acid and/or sodium hydroxide for pH adjustment
Water for injections.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After first opening the bottle the in-use shelf life is 3 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.
Store in the original carton in order to protect from light.

After first opening the bottle:
Do not store above 25°C. Do not freeze.
Store the bottle in the original carton in order to protect from light.

6.5 Nature and contents of container

Transparent low-density polyethylene (LDPE) bottle with white ophthalmic squeeze dispenser (OSD) (polyethylene, polypropylene, cyclic olefin copolymer (COC)) with blue polyethylene cap containing tamper evident system.

The following pack sizes are available: cartons containing 1 or 3 bottles of 3 ml (each intended for 1 month patient's in-use period), 1 bottle of 5 ml (for 2 months), or 1 bottle of 7 ml (for 3 months).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Santen OY
Niittyhaankatu 20
FI-33720 Tampere
Finland

8 MARKETING AUTHORISATION NUMBER

PA0879/003/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th December 2020

10 DATE OF REVISION OF THE TEXT

March 2022