SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Saflutan 15 micrograms/ml eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 15 micrograms of tafluprost
One drop contains about 0.45 micrograms of tafluprost.

Excipient with known effect: One ml of eye drops solution contains 1.2 mg phosphates and one drop contains approximately 0.04 mg phosphates.

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 between 5.5 and 6.7, and an osmolality of 260 - 310 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of elevated intraocular pressure in open angle glaucoma and ocular hypertension.

As monotherapy in patients:

- who would benefit from preservative free eye drops
- insufficiently responsive to first line therapy
- intolerant or contra-indicated to first line therapy

As adjunctive therapy to beta-blockers.

Saflutan is indicated in adults ≥ 18 years.

4.2 Posology and method of administration

Posology
The recommended dose is one drop of Saflutan in the conjunctival sac of the affected eye(s) once daily in the evening.

The dose should not exceed once daily as more frequent administration may lessen the intraocular pressure lowering effect.

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

Paediatric population:
The safety and efficacy of tafluprost in children below age 18 has not yet been established. No data are available.

Use in renal/hepatic impairment:
Tafluprost has not been studied in patients with renal/hepatic impairment and should therefore be used with caution in such patients.

Method of administration
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. Otherwise the unpreserved alternative of the same medicinal product in single dose-units may be more appropriate.

To prevent potential contamination of the solution, the patients should 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.
To reduce the risk of darkening of the eyelid skin the patients should wipe off any excess solution from the skin. As with any other eye drops, nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route.

There will be a residual volume of approximately 1 ml, which cannot be dosed. The patient should not try to empty the bottle.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation. 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.

There is no experience in patients with severe asthma. Such patients should therefore be treated with caution.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions are anticipated in humans, since systemic concentrations of tafluprost are extremely low following ocular dosing. Therefore, specific interaction studies with other medicinal products have not been performed with tafluprost.

In clinical studies tafluprost was used concomitantly with timolol without evidence of interaction.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception
Saflutan must not be used in women of childbearing age/potential unless adequate contraceptive measures are in place (see section 5.3).

Pregnancy
There are no adequate data from 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). Therefore, Saflutan should not be used during pregnancy unless clearly necessary (in case no other treatment options are available).

Breastfeeding
It is unknown whether tafluprost and/or its metabolites are excreted in human milk. A study in rats has shown excretion of tafluprost and/or its metabolites in breast milk after topical administration (see section 5.3).
Therefore tafluprost should not be used during breastfeeding.

Fertility
In female and male rats, mating performance and fertility was unaffected by intravenous tafluprost doses up to 100 microg/kg/day.

4.7 Effects on ability to drive and use machines

Tafluprost has minor influence on the ability to drive and use machines. If transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

In clinical studies, over 1,400 patients have been treated with preserved tafluprost either as monotherapy or as adjunctive therapy to timolol 0.5%. The most frequently reported treatment-related adverse event was ocular hyperaemia. It occurred in approximately 13% of the patients participating in the clinical studies with preserved tafluprost in Europe and the US. It was mild in most cases and led to discontinuation on an average in 0.4% of patients participating in the pivotal studies. In a 3-month, phase III study in the US comparing the non-preserved formulation of tafluprost with the non-preserved timolol formulation, ocular hyperemia occurred in 4.1% (13/320) of patients treated with tafluprost.

The following undesirable effects related to treatment were reported during clinical trials with tafluprost in Europe and the US after a maximum follow-up of 24 months:

Within each frequency grouping, adverse reactions are presented in order of decreasing frequency.

Nervous system disorders

Common (≥1/100 to <1/10): headache

Eye disorders

Common (≥1/100 to <1/10): eye pruritus, eye irritation, eye pain, conjunctival/ocular hyperaemia, changes in eyelashes (increased length, thickness and number of lashes), dry eye, foreign body sensation in eyes, eyelash discolouration, erythema of eyelid, superficial punctate keratitis (SPK), photophobia, increased lacrimation, blurred vision, reduced visual acuity and increased iris pigmentation.

Uncommon (≥1/1,000 to <1/100): blepharal pigmentation, eyelid oedema, asthenopia, conjunctival oedema, eye discharge, blepharitis, anterior chamber cells, ocular discomfort, anterior chamber flare, conjunctival pigmentation, conjunctival follicles, allergic conjunctivitis and abnormal sensation in eye.

Not known (cannot be estimated from the available data): iritis/uveitis, lid sulcus deepened, macular oedema/cystoid macular oedema.

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.

Respiratory, thoracic, and mediastinal disorders

Not known (cannot be estimated from the available data): exacerbation of asthma, dyspnea

Skin and subcutaneous tissue disorders

Uncommon (≥1/1,000 to <1/100): hypertrichosis of eyelid

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 Yellow Card Scheme,

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdose is unlikely to occur after ocular administration.

If overdose occurs, treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, prostaglandin analogues

ATC code: S01EE05

Mechanism of action

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. Tafluprost acid has a 12-fold higher affinity for the FP receptor than latanoprost. Pharmacodynamic studies in monkeys indicate that tafluprost reduces intraocular pressure by increasing the uveoscleral outflow of aqueous humour.

Pharmacodynamic effects

The experiments in normotensive and ocular hypertensive monkeys showed that tafluprost is an effective IOP-lowering compound. In the study investigating IOP-reducing effect of tafluprost metabolites only tafluprost acid reduced IOP significantly.

When rabbits were treated for 4 weeks with a tafluprost 0.0015% ophthalmic solution once daily, the optic nerve head blood flow was significantly (15%) increased compared to baseline when measured by the laser speckle flowgraphy on Days 14 and 28.

Clinical efficacy

Reduction of the intraocular pressure starts between 2 and 4 hours after the first administration and maximum effect is reached at around 12 hours after instillation. The duration of effect is maintained for at least 24 hours. Pivotal studies with a tafluprost formulation containing the preservative benzalkonium chloride have demonstrated that tafluprost is effective as monotherapy and showedan additive effect when administered as adjunctive therapy to timolol: In a 6-month study, tafluprost showed a significant IOP-lowering effect of 6 to 8 mmHg at different time points of the day as compared to 7 to 9 mmHg with latanoprost. In a second 6-month clinical study, tafluprost reduced IOP by 5 to 7 mmHg as compared to 4 to 6 mmHg with timolol. The IOP-lowering effect of tafluprost was maintained in the extension of these studies up to 12 months. In a 6-week study, the IOP-lowering effect of

tafluprost was compared with its vehicle when used adjunctively with timolol. Compared to baseline values (measured after a 4-week run in on timolol), the additional IOP-lowering effects were 5 to 6 mmHg in the timolol-tafluprost group and 3 to 4 mmHg in the timolol-vehicle group. The preserved and the non-preserved formulations of tafluprost showed a similar IOP-lowering effect of over 5 mmHg in a small cross-over study with a 4-week treatment period. Furthermore, in a 3-month study in the US comparing the non-preserved formulation of tafluprost with the non-preserved formulation of timolol, the IOP-lowering effect of tafluprost was between 6.2 and 7.4 mmHg at different timepoints whereas that of timolol varied between 5.3 and 7.5 mmHg.

5.2 Pharmacokinetic properties

Absorption

After once daily administration of one drop of unpreserved tafluprost 0.0015% eye drops to both eyes for 8 days, plasma concentrations of tafluprost acid were low and had similar profiles on days 1 and 8. The plasma concentrations peaked at 10 minutes after dosing and declined to below the lower limit of detection (10 pg/ml) before one hour after dosing. Mean C_{max} (26.2 and 26.6 pg/ml) and $AUC_{0\text{-last}}$ (394.3 and 431.9 pg*min/ml) values were similar on days 1 and 8, indicating that a steady drug concentration was reached during the first week of ocular dosing. No statistically significant differences in the systemic bioavailability between the preserved and unpreserved formulation were detected.

In a rabbit study, the absorption of tafluprost into the aqueous humour was comparable after a single ocular instillation of unpreserved or preserved tafluprost 0.0015% ophthalmic solution.

Distribution

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.

Biotransformation

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.

Elimination

Following once daily administration of ^{3}H-tafluprost (0.005% ophthalmic solution; 5 microl/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.

5.3 Preclinical safety data

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 the drug and natural prostaglandins, the oral bioavailability is expected to be very low.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol

Sodium dihydrogen phosphate dihydrate

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: 3 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C -8°C). Do not freeze.
After opening: Store below 25°C.

Store in the original carton in order to protect from light.

6.5 Nature and contents of container

Transparent low-density polyethylene (LDPE) bottles with white Aptar OSD (polyethylene, polypropylene, cyclic olefin copolymer) with blue polyethylene cap. Each bottle has a fill volume of 3 ml, 5 ml or 7 ml.

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

33720 Tampere

Finland

8 MARKETING AUTHORISATION NUMBER(S)

PL 16058/0026

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/09/2024

10 DATE OF REVISION OF THE TEXT

03/09/2024