PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrSAFLUTAN™

Tafluprost Ophthalmic Solution

Ophthalmic Solution (Preservative-Free), 15 mcg/mL, Ophthalmic

Elevated Intraocular Pressure Therapy

Fluorinated $PGF_{2\alpha}$ Analogue

Purdue Pharma
575 Granite Court
Pickering, ON
L1W 3W8

Date of Initial Approval:
November 3, 2016

Date of Revision:
July 29, 2020

Submission Control No: 237802

RECENT MAJOR LABEL CHANGES

Not applicable

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SAFLUTAN™ (tafluprost ophthalmic solution, 15 mcg/mL) is indicated for:

- the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): No overall clinical differences in efficacy or adverse events profile have been observed between elderly (> 65 years) and non-elderly (≤ 65 years) patients.

2 CONTRAINDICATIONS

Tafluprost is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose and Dosage Adjustment

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use.

Adults (≥18 years of age): 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 of prostaglandin analogues may lessen the intraocular pressure lowering effect and increase the frequency and severity of adverse events.

Reduction of the intraocular pressure starts approximately 2 to 4 hours after the first administration with the maximum effect reached after 12 hours.

Geriatrics (> 65 years of age): No dosage adjustment is required for elderly patients.

3.2 Administration

SAFLUTAN is a sterile solution that does not contain a preservative. For single use only, one

container is sufficient to treat both eyes. Any unused solution should be discarded immediately after use.

SAFLUTAN may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug product is being used, each one should be administered at least 5 minutes apart.

To reduce the risk of darkening of the eyelid skin patients should blot 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 products administered via the ocular route.

Contact lenses should be removed prior to the administration of SAFLUTAN, and may be reinserted 15 minutes following administration.

The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be maintained after the individual unit is opened, the remaining contents should be discarded immediately after administration.

3.3 Missed Dose

If a dose is missed at its usual time, a single drop should be used as soon as possible, and then the next dose should be administered at the usual time. A double dose should not be given.

4 OVERDOSAGE

For management of a suspected drug overdose, particularly an accidental oral ingestion, contact your regional Poison Control Centre.

No case of overdose has been reported. Overdose is unlikely to occur after ocular administration. If overdose with SAFLUTAN (tafluprost ophthalmic solution, 15 mcg/mL), occurs, treatment should be symptomatic.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Ophthalmic	Solution, each mL contains 15 mcg tafluprost	disodium edetate, glycerol, polysorbate 80, sodium dihydrogen phosphate dihydrate, and hydrochloric acid and/or sodium hydroxide.

Dosage Form
SAFLUTAN (tafluprost ophthalmic solution, 15 mcg/mL) is supplied as a sterile solution in single–dose containers. One single-dose container (0.3 mL solution) contains 4.5 mcg of tafluprost. Ten single-dose (2 strips of 5 each) individual unit dose pipettes are provided in one foil pouch. There are 30 pipettes per carton.

Composition
SAFLUTAN (tafluprost ophthalmic solution, 15 mcg/mL) is a clear, colorless, buffered, sterile solution with a pH range of 5.5 - 6.7 and an Osmolality range of 260 - 300 mOsmol/kg.

6 WARNINGS AND PRECAUTIONS

General
Tafluprost ophthalmic solution (15 mcg/mL) has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. 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 (See ADVERSE REACTIONS).

Carcinogenesis and Mutagenesis
See Toxicology.

Driving and Operating Machinery
As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

Contact lenses should be removed prior to the administration of SAFLUTAN, and may be reinserted 15 minutes following administration.

Hepatic
Hepatic Insufficiency
SAFLUTAN has not been studied in patients with hepatic insufficiency and should therefore be used with caution in such patients.

Ophthalmologic
Eyelash Changes
SAFLUTAN may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, color, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes (trichiasis). Eyelash changes are usually reversible upon discontinuation of treatment.

Eyelid Skin Darkening
Eyelid skin darkening has been reported in association with the use of SAFLUTAN. Studies with other prostaglandin analogues indicate that eyelid skin darkening is usually reversible upon discontinuation of treatment.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes. These changes in pigmentation and eyelash growth may be permanent. The long term effects of increased pigmentation are not known.

Intraocular Inflammation
Caution is recommended in patients with known risk factors for iritis/uveitis and should generally not be used in patients with active intraocular inflammation.

Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin F2α analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular edema. Therefore, caution is recommended when using tafluprost in these patients.

Pigmentation
SAFLUTAN may gradually cause changes to pigmented tissues. Pigmentation is expected to increase as long as tafluprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of tafluprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. **The long term effects of increased pigmentation are not known**.

The change in iris pigmentation occurs slowly and may not be noticeable for several months. The change in eye color has predominantly been seen in patients with mixed colored irises, e.g. blue-brown, grey-brown, yellow-brown and green-brown. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with SAFLUTAN can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Renal
Renal Insufficiency
SAFLUTAN has not been studied in patients with renal insufficiency and should therefore be used with caution in such patients.

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

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.

Pulmonary Insufficiency
SAFLUTAN has not been systematically studied in patients with pulmonary insufficiency and should therefore be used with caution in such patients.

6.1 Special Populations

6.1.1 Pregnant Women

There are no adequate and well-controlled studies of tafluprost ophthalmic solution (15 mcg/mL) performed in pregnant women. Tafluprost-related effects were observed in embryo-fetal

developmental studies in animals (see below). Although results from animal studies are not always predictive of human response, SAFLUTAN should not be used during pregnancy or by women attempting to become pregnant unless the potential benefit justifies the potential risk to the fetus.

Women of childbearing age/potential should have adequate contraceptive measures in place. In embryo-fetal development studies in rats and rabbits, tafluprost administered intravenously caused increases in post-implantation losses in rats and rabbits and reductions in fetal body weights in rats. Tafluprost also increased the incidence of vertebral skeletal abnormalities in rats and the incidence of skull, brain and spine malformations in rabbits. In rats, there were no adverse effects on embryo-fetal development at a dose of 3 mcg/kg/day corresponding to maternal plasma levels of tafluprost acid that were 343-times the maximum clinical exposure based on Cmax. In rabbits, effects were seen at tafluprost dose of 0.03 mcg/kg/day corresponding to maternal plasma levels of tafluprost acid during the critical period of development that were 5.3-times higher than the clinical exposure based on Cmax. At the no effect dose in rabbits (0.01 mcg/kg/day), maternal plasma levels of tafluprost acid were below the lower level of quantification (20 pg/mL).

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 no observed adverse effect level was at a tafluprost intravenous dose of 0.3 mcg/kg/day which is greater than 3 times the maximum recommended clinical dose based on body surface area comparison.

6.1.2 Breast-feeding

It is unknown whether SAFLUTAN or its metabolites are excreted in human milk. A study in lactating rats demonstrated that radiolabeled tafluprost and/or its metabolites (0.1% of the dose) were excreted in milk. Because many drugs are excreted in human milk, caution should be exercised when SAFLUTAN is administered to a nursing woman.

6.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

6.1.4 Geriatrics

Geriatrics (>65 years of age): No overall clinical differences in efficacy or adverse events profile have been observed between elderly (> 65 years) and non-elderly (≤ 65 years) patients. Therefore, no dosage adjustment is required for elderly patients.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

Tafluprost has been studied in 905 patients in five randomized, double-masked, parallel group, multicenter, monotherapy, active-controlled studies, up to 24 months in duration, primarily using a preservative-containing formulation. The most commonly reported adverse reactions were similar in all studies. The most common drug-related adverse reaction in patients treated with

tafluprost was conjunctival hyperemia, which was reported in 4 to 20% of patients. Most adverse reactions were mild. Adverse drug reactions led to discontinuation in 1.7% of patients participating in these studies.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety assessment of SAFLUTAN is based on the pooled safety data from five randomized clinical studies using tafluprost (administered once daily) and active comparators as controls (either latanoprost or timolol) in patients with primary open-angle glaucoma or ocular hypertension. The pooled safety data are a summation of all the adverse reactions for the total duration of each study (i.e., 4-week data for study 15-002, 6-week data for study 74457, 3-month data for study 001, 12-month data for study 15-003 and 24-month data for study 74458).

The following drug-related adverse reactions, as determined by the investigator, were reported at ≥ 1% in the overall population receiving the clinical dose of tafluprost during treatment from 4-weeks up to 24 months.

Table 2 - Number (%) of Patients with Tafluprost Drug-Related[a] Adverse Events (≥ 1%) Protocols 15-002, 74457, 74458, 15-003 and 001

Adverse Event	Tafluprost 0.0015% (N[b]=905) n[c]	(%)	Timolol Maleate 0.5% (N[b]=543) n[c]	(%)	Latanoprost 0.005% (N[b]=311) n[c]	(%)
Eye disorders						
Conjunctival hyperemia	28	(3.1)	4	(0.7)	6	(1.9)
Conjunctival redness	12	(1.3)	0	(0.0)	2	(0.6)
Eye redness	33	(3.6)	12	(2.2)	7	(2.3)
Ocular hyperemia	17	(1.9)	2	(0.4)	2	(0.6)
Dry eye	20	(2.2)	7	(1.3)	7	(2.3)
Eyelash darkening	14	(1.5)	0	(0.0)	9	(2.9)
Foreign body sensation in eyes	12	(1.3)	5	(0.9)	5	(1.6)
Growth of eyelashes	21	(2.3)	0	(0.0)	11	(3.5)
Ocular pain	25	(2.8)	11	(2.0)	6	(1.9)
Burning eyes	29	(3.2)	13	(2.4)	12	(3.9)
Eye irritation	11	(1.2)	7	(1.3)	4	(1.3)
Eyes stinging	14	(1.5)	10	(1.8)	4	(1.3)
Ocular pruritus	34	(3.8)	9	(1.7)	4	(1.3)

Photophobia	14	(1.5)	3	(0.6)	2	(0.6)
Nervous system disorder						
Headache	14	(1.5)	4	(0.7)	3	(1.0)

a. Determined by the investigator to be possibly, probably or definitely drug-related.

b. N = Number of patients in the treatment group.

c. n = Number of patients with the corresponding adverse event.

7.3 Less Common Clinical Trial Adverse Reactions (<1%)

Eye disorders:

Uncommon (≥1/1 000 to <1/100): abnormal sensation in eye, anterior chamber cell, anterior chamber flare, blepharal pigmentation, blepharitis, bloodshot eye, cataract, cataract cortical, cataract nuclear, chemosis, conjunctival disorder, conjunctival follicles, conjunctival pigmentation, deposit eye, epiphora, erythema of eyelid, eye ache, eye discharge, eyelash thickening, eyelid oedema, eyelids pruritus, eyes tearing, hyperaemia eyelid, iris hyperpigmentation, lacrimation, ocular discomfort, punctate keratitis, scotoma, superficial punctate keratitis, swollen eyelid, tired eyes, vision blurred, vision decreased, visual acuity reduced, visual field constriction, visual field defect, xerophthalmia

Very Rare (<1/10,000): 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

Gastrointestinal disorders:

Uncommon (≥1/1 000 to <1/100): dry mouth

Respiratory, thoracic and mediastinal disorders:

Uncommon (≥1/1 000 to <1/100): cough, sore throat

Skin and subcutaneous tissue disorders:

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

Since the first market authorization, preservative-free tafluprost 0.0015% was evaluated in a twelve-week, randomized, double-masked, active-controlled clinical study (N=320), no new drug-related adverse reactions were reported (incidence ≥ 1%). The drug-related incidence of conjunctival hyperemia was 4.1%.

7.4 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of SAFLUTAN.

Eye disorders: Allergic conjunctivitis, deepening of the eyelid sulcus, iritis/uveitis, corneal erosion, retinal detachment, conjunctivitis

Nervous system disorders: Dizziness

Respiratory, thoracic and mediastinal disorders: Exacerbation of asthma, dyspnea

Immune system disorders: Hypersensitivity reactions, including anaphylactic shock

8 DRUG INTERACTIONS

8.1 Overview

No drug-drug interactions are anticipated in humans, since systemic concentrations of tafluprost acid are extremely low (<30 pg/mL) and transient (not quantifiable (<10 pg/mL) at ≥30 minutes following ocular dosing). Therefore, specific drug interaction studies have not been performed with tafluprost.

8.2 Drug-Drug Interactions

Interactions with other drugs have not been studied. In clinical studies tafluprost was used concomitantly with timolol without evidence of an increase in the incidence of adverse events.

8.3 Drug-Food Interactions

Interactions with food have not been established.

8.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 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.

In preclinical studies tafluprost has been shown to reduce IOP in non-human primates. Studies of aqueous humor dynamics in primates indicate that the main mechanism of action for IOP reduction is increased uveoscleral outflow of aqueous humor. The effects of tafluprost on aqueous humor dynamics have not been studied in humans.

9.2 Pharmacodynamics

Dose response and dose regimen
Two dose-finding studies evaluated the effects of tafluprost given once daily (evening) in patients with elevated IOP. In the first study tafluprost 0.001%, 0.0025%, and 0.005% were tested using placebo and latanoprost as negative and positive controls, respectively. In the second study, tafluprost 0.0015% was tested, along with 0.0003%, and 0.0025%, with two positive control groups: 0.005% latanoprost and 0.5% timolol. IOP was measured up to 24-hours post-dose for both studies. From these studies, the duration of action for tafluprost was found to be beyond 24 hours.

An additional study evaluated the duration of action of 0.0015% tafluprost up to 48 hours compared with latanoprost. The mean IOP at 12 hours after the last dose administered during the study was 17 mmHg, and remained stable for up to 24 hours after the last dose.

Based on this information, a once-daily evening dosing of 0.0015% tafluprost was determined to be optimal.

Cardiovascular effects
Tafluprost in clinical doses has not been found to have any significant pharmacological effects on the cardiovascular system.

9.3 Pharmacokinetics

Absorption: Tafluprost is absorbed through the cornea where the isopropyl ester is hydrolyzed to the biologically active acid metabolite (EC_{50} to the recombinant human FP prostanoid receptor = 217 pg/mL). Pharmacokinetics of tafluprost acid were obtained from a study comparing preservative-containing and preservative-free ophthalmic solutions. The preservative-free formulation showed similar pharmacokinetic properties to the preservative-containing formulation. Mean plasma C_{max} and $AUC_{0\text{-last}}$ values for the preservative-containing and preservative-free formulations on Days 1 and 8 are shown in Table . Mean plasma concentrations were below the limit of quantification at 30 minutes for both formulations.

Table 3 - Mean Tafluprost Acid Pharmacokinetic Parameters ($AUC_{0\text{-last}}$ and C_{max}) on Days 1 and 8 Following Once Daily Dosing of Tafluprost 0.0015% (N=16)

Formulation	Study Day	$AUC_{0\text{-last}}$ (pg*min/mL)	Cmax (pg/mL)
Preserved	Day 1	406	24
Preserved	Day 8	581	31
Unpreserved	Day 1	394	26
Unpreserved	Day 8	432	27

In a rabbit study, the absorption of tafluprost into the aqueous humor was comparable after a single ocular instillation of preservative-free or preservative-containing tafluprost 0.0015% ophthalmic solution.

Distribution: After topical administration of 1mcg ^{3}H-tafluprost on the monkey eye, the maximum radioactivity in the aqueous humor was detected at 2 hours (21-30 ng equivalents/mL) and declined to 0.3-0.4 ng equivalents/mL at 24 hours.

The binding of tafluprost acid to human serum albumin was >99%. It is anticipated that tafluprost acid will be highly protein bound in human plasma.

Metabolism: Tafluprost, an ester prodrug, is hydrolyzed to its biologically active acid metabolite in the eye. The acid metabolite is further metabolized via fatty acid β-oxidation and phase II conjugation.

Cytochrome P450 (CYP) enzyme system is not involved in the metabolism of tafluprost acid.

Excretion: In two clinical studies, mean tafluprost acid metabolite concentrations fell below the limit of quantification in plasma (10 pg/mL) 30 minutes after administration, indicating rapid elimination.

Special Populations and Conditions

***Hepatic Insufficiency*:** Tafluprost has not been studied in patients with hepatic insufficiency and should therefore be used with caution in such patients.

Renal Insufficiency: Tafluprost has not been studied in patients with renal insufficiency and should therefore be used with caution in such patients.

Pulmonary Insufficiency: Tafluprost has not been systematically studied in patients with pulmonary insufficiency and should therefore be used with caution in such patients.

10 STORAGE, STABILITY AND DISPOSAL

Store the unopened foil pouches of SAFLUTAN (tafluprost ophthalmic solution, 15 mcg/mL), in a refrigerator (2°C – 8°C).

Shelf life unopened foil pouch: 36 months
Shelf life opened foil pouch: 28 days

After opening the foil pouch:

- Keep the single-dose containers in the original foil pouch.
- Do not store above 25°C.
- Discard any unused single-dose containers after 28 days from date of first opening of the foil pouch.
- Discard an opened single-dose container with any remaining solution immediately after use.
- Keep in a safe place out of the reach of children.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

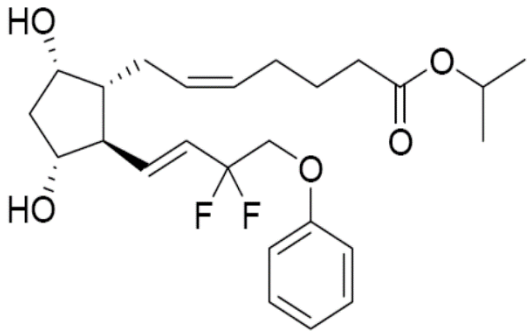
Drug Substance

Proper name: tafluprost

Chemical name: 1-methylethyl (5Z)-7[(1R, 2R, 3R, 5S)-2-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxycyclopentyl]-5- heptenoate

Molecular formula and molecular mass: $C_{25}H_{34}F_2O_5$
452.53

Structural formula:



Physicochemical properties: Tafluprost is a colorless to light yellow viscous liquid that is practically insoluble in water.

12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

Table 4 - Summary of Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range) (Years)	Gender

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range) (Years)	Gender
001	Multicenter, randomized, double- masked, active-controlled, parallel-group	Tafluprost 0.0015% QD (preservative-free) Timolol 0.5% BID (preservative-free) Ophthalmic; one drop in the affected eye(s) according to the regimen above 12 weeks	Tafluprost (n=320) Timolol (n=323)	Tafluprost: 63.3 (range 25-91) Timolol: 63.3 (range 21-94)	Male: 268 Female: 375
74458	Multicenter, randomized, double-masked, active-controlled, parallel-group	Tafluprost 0.0015% Latanoprost 0.005% Ophthalmic; one drop in the affected eye(s) according to the regimen above 24 months	Tafluprost (n=269) Latanoprost (n=264)	Tafluprost: 62.5 (range 23-86) Latanoprost: 62.4 (range 18-88)	Male: 221 Female: 312
15-003	Multicenter, randomized, double-masked, active-controlled, parallel-group	Tafluprost 0.0015% QD Timolol 0.5% BID Ophthalmic; one drop in the affected eye(s) according to the regimen above 12 months	Tafluprost (n=267) Timolol (n=191)	Tafluprost: 61.3 (range 21-88) Timolol: 61.5 (range 21-84)	Male: 187 Female: 271

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range) (Years)	Gender
77550	Multicenter, randomized, investigator-masked, crossover	Tafluprost 0.0015 % (preserved) Tafluprost 0.0015 % (preservative-free) Ophthalmic; one drop in the affected eye(s) according to the regimen above 4 weeks	Tafluprost preserved-preservative-free sequence (n=21) Tafluprost preservative-free-preserved sequence (n=22)	65.3 (range 35-85)	Male: 16 Female: 27
77552	Multicenter, open-label	Tafluprost 0.0015% QD (preservative-free) Ophthalmic; one drop in the affected eye(s) according to the regimen above 12 weeks	Tafluprost unpreserved (n=158)	68.9 (range 37-88)	Male: 54 Female: 104

12.2 Study Results

Clinical Effects on Intraocular Pressure

The efficacy of tafluprost as monotherapy was investigated in clinical studies of up to two years duration in patients with primary open-angle glaucoma or ocular hypertension.

Reduction of 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.

Monotherapy vs. Active Comparators

The efficacy of tafluprost as monotherapy in patients with primary open-angle glaucoma or ocular hypertension (baseline IOP ≥22 mmHg) was demonstrated in three large clinical studies of up to two years duration. The primary efficacy endpoint of the studies was the intraocular pressure (IOP) change from baseline. The IOP-lowering effect of tafluprost was demonstrated throughout the day and this effect was maintained during long-term administration.

In a 12-week randomized, double-masked, active-controlled, parallel-group, multinational study (baseline IOP range of 23 to 36 mmHg), preservative-free tafluprost 0.0015% q.d. (N=320)

reduced IOP from baseline by 6 to 9 mmHg throughout the study as compared to 5 to 8 mmHg with preservative-free timolol 0.5% b.i.d. (N=323). The IOP-lowering effect of tafluprost was non-inferior to that of timolol at all visits and time points.

Table 5 - IOP by Visit and Time Point (Protocol 001)

Visit	Time Point	Tafluprost 0.0015%			Timolol Maleate 0.5%		
		N[a]	Mean (SD) mmHg	Change (% Change)[b]	N[a]	Mean (SD) mmHg	Change (% Change)[b]
Baseline	8:00	299	26.1 (2.7)	--	313	26.0 (2.5)	--
	10:00	299	24.8 (3.3)	--	313	24.6 (2.9)	--
	16:00	296	23.8 (3.3)	--	312	23.5 (3.1)	--
Week 2	8:00	280	18.9 (3.1)	-7.1 (-27.3)	295	19.2 (3.3)	-6.8 (-25.8)
	10:00	293	18.0 (2.9)	-6.8 (-27.2)	305	18.5 (3.2)	-6.1 (-24.1)
	16:00	292	17.5 (3.1)	-6.2 (-25.7)	303	18.3 (3.0)	-5.3 (-21.7)
Week 6	8:00	294	18.8 (3.0)	-7.3 (-27.7)	308	18.6 (3.2)	-7.4 (-28.1)
	10:00	298	17.7 (3.1)	-7.0 (-28.1)	312	18.0 (3.0)	-6.6 (-26.2)
	16:00	298	17.3 (3.2)	-6.3 (-26.3)	311	18.1 (3.0)	-5.5 (-22.7)
Week 12	8:00	296	18.6 (3.1)	-7.4 (-28.5)	308	18.5 (3.2)	-7.5 (-28.5)
	10:00	298	17.7 (2.9)	-7.0 (-28.3)	312	18.0 (3.2)	-6.6 (-26.4)
	16:00	298	17.4 (2.9)	-6.2 (-25.9)	311	17.9 (3.2)	-5.7 (-23.3)

a. N = Number of patients included in the analysis at the corresponding visit and time point.

b. Mean absolute change (mmHg) and percentage change (%) from baseline.

Analysis details: Per-protocol population; Analysis of covariance; Worse eye.

In a 6-month randomized, double-masked, active-controlled, parallel-group, multinational study (baseline IOP range of 22 to 34 mmHg), tafluprost 0.0015% q.d. (N=269) showed a significant IOP-lowering effect from baseline of 7 to 8 mmHg at Month 6 as compared to 7 to 9 mmHg with latanoprost 0.005% q.d. (N=264). The IOP-lowering effect of tafluprost was sustained in the extension of this study up to 24 months. However, tafluprost did not reach the predetermined criterion for non-inferiority versus latanoprost.

Table 6 - IOP by Visit and Time Point (Protocol 74458)

Visit	Time Point	Tafluprost 0.0015%			Latanoprost 0.005%		
		N[a]	Mean (SD) mmHg	Change (% Change)[b]	N[a]	Mean(SD) mmHg	Change (% Change)[b]
Baseline	8:00	264	25.8 (2.9)	--	264	25.3 (2.9)	--
	12:00	264	24.5 (3.4)	--	264	24.2 (3.0)	--
	16:00	263	23.6 (3.7)	--	264	23.1 (3.5)	--
	20:00	264	23.2 (3.7)	--	264	22.8 (3.6)	--
Week 2	8:00	264	17.7 (3.3)	-8.1 (-31.4)	264	16.7 (3.2)	-8.6 (-33.7)
Week 6	8:00	263	17.8 (3.4)	-8.0 (-30.8)	260	16.6 (3.0)	-8.7 (-34.0)
Month 3	8:00	254	17.6 (3.3)	-8.3 (-31.8)	256	16.2 (2.9)	-9.1 (-35.7)
	12:00	252	17.1 (3.1)	-7.3 (-29.5)	256	15.8 (2.9)	-8.4 (-34.3)
	16:00	250	16.7 (3.0)	-6.9 (-28.4)	254	15.9 (2.8)	-7.2 (-30.5)
	20:00	252	16.8 (2.9)	-6.3 (-26.3)	255	15.8 (2.8)	-7.0 (-29.8)
Month 6	8:00	244	17.8 (3.5)	-8.1 (-31.0)	251	16.1 (3.0)	-9.2 (-35.9)
	12:00	242	17.3 (3.2)	-7.1 (-28.6)	251	15.7 (2.9)	-8.5 (-34.3)
	16:00	243	17.0 (3.1)	-6.7 (-27.5)	248	15.6 (2.9)	-7.5 (-31.8)
	20:00	243	16.8 (3.1)	-6.3 (-26.5)	248	15.8 (2.7)	-7.1 (-30.0)
Month 9	8:00	242	18.0 (3.6)	-7.8 (-30.0)	250	16.4 (2.9)	-8.9 (-34.8)
Month 12	8:00	227	18.1 (3.7)	-7.6 (-29.4)	247	16.3 (3.0)	-9.0 (-35.1)
	12:00	224	17.3 (3.4)	-7.0 (-28.3)	246	15.9 (3.0)	-8.3 (-33.7)
	16:00	222	17.2 (3.4)	-6.2 (-25.7)	244	15.7 (3.0)	-7.3 (-30.8)
	20:00	220	17.2 (3.4)	-5.8 (-24.2)	243	16.0 (3.3)	-6.7 (-28.5)
Month 15	8:00	192	17.4 (3.5)	-8.2 (-31.8)	224	15.8 (2.7)	-9.4 (-36.9)
Month 18	8:00	188	17.2 (3.4)	-8.4 (-32.7)	220	15.9 (3.2)	-9.3 (-36.4)
	12:00	186	16.6 (3.1)	-7.5 (-30.5)	218	15.9 (3.0)	-8.2 (-33.4)
	16:00	185	16.5 (3.1)	-6.9 (-28.8)	219	15.6 (3.0)	-7.3 (-31.0)
	20:00	184	16.5 (3.1)	-6.4 (-27.0)	218	15.7 (3.1)	-6.8 (-29.2)
Month 24	8:00	185	17.6 (4.0)	-8.0 (-31.3)	217	16.1 (2.9)	-9.0 (-35.4)
	12:00	186	16.9 (3.7)	-7.2 (-29.4)	216	15.8 (2.9)	-8.2 (-33.6)
	16:00	183	16.8 (3.4)	-6.6 (-27.4)	216	15.9 (2.9)	-7.0 (-29.7)
	20:00	181	16.7 (3.4)	-6.3 (-26.5)	212	15.8 (2.9)	-6.6 (-28.5)

a. N = Number of patients included in the analysis at the corresponding visit and time point.

b. Mean absolute change (mmHg) and percentage change (%) from baseline.

Analysis details: Intention-to-treat population; Repeated measurements analysis of covariance; Worse eye.

In a second 6-month randomized, double-masked, active-controlled, parallel-group, multicenter clinical study conducted in the U.S. (baseline IOP range of 22 to 34 mmHg), tafluprost 0.0015% q.d. (N=267) and timolol 0.5% b.i.d. (N=191) each reduced IOP from baseline by 5 to 7 mmHg at Month 6. The IOP-lowering effect of tafluprost was sustained in the extension of this study up to 12 months and was non-inferior to that of timolol at all visits and time points.

Table 7 - IOP by Visit and Time Point (Protocol 15-003)

Visit	Time Point	Tafluprost 0.0015%			Timolol Maleate 0.5%		
		N[a]	Mean (SD) mmHg	Change (% Change)[b]	N[a]	Mean (SD) mmHg	Change (% Change)[b]
Baseline	8:00	265	25.6 (3.1)	--	187	25.6 (3.2)	--
	10:00	265	23.5 (3.6)	--	187	23.8 (3.8)	--
Week 2	8:00	265	18.6 (3.3)	-7.0 (-26.8)	187	19.1 (3.4)	-6.5 (-25.0)
	10:00	77	17.4 (3.0)	-6.1 (-24.8)	62	17.7 (2.9)	-5.9 (-23.9)
Week 6	8:00	260	18.6 (3.2)	-7.1 (-27.2)	185	18.6 (3.5)	-6.9 (-26.8)
	10:00	141	17.3 (3.2)	-5.7 (-24.0)	105	17.5 (3.1)	-6.0 (-24.5)
Month 3	8:00	257	19.0 (3.4)	-6.7 (-25.8)	180	19.3 (3.9)	-6.3 (-24.4)
	10:00	257	17.8 (3.2)	-5.7 (-23.7)	179	17.9 (3.5)	-5.9 (-24.1)
Month 6	8:00	251	19.0 (3.4)	-6.6 (-25.4)	171	19.0 (3.7)	-6.5 (-25.2)
	10:00	251	17.9 (3.3)	-5.5 (-22.9)	172	18.0 (3.4)	-5.6 (-23.1)
Month 9	8:00	247	18.4 (3.3)	-7.2 (-27.8)	165	18.9 (3.3)	-6.5 (-25.3)
	10:00	246	17.7 (3.2)	-5.8 (-24.0)	165	18.0 (3.3)	-5.5 (-22.6)
Month 12	8:00	240	18.9 (3.5)	-6.7 (-25.7)	162	18.5 (3.1)	-6.8 (-26.7)
	10:00	239	17.8 (3.4)	-5.6 (-23.0)	159	17.8 (3.3)	-5.5 (-22.7)

a. N = Number of patients included in the analysis at the corresponding visit and time point.

b. Mean absolute change (mmHg) and percentage change (%) from baseline.

Analysis details: Intention-to-treat population; Repeated measurements analysis of covariance; Worse eye.

Preservative-free vs. Preservative-containing

In a small 4-week randomized, investigator-masked, multinational crossover study (baseline IOP range of 22 to 34 mmHg), the IOP-lowering effect of preservative-free tafluprost 0.0015% q.d. was compared with the preservative-containing formulation (N=43). Patients were dosed for 4 weeks with the preservative-free and for 4 weeks with the preservative-containing formulation in crossover fashion, with an intervening washout period. Compared to baseline values, the

preservative-containing and the preservative-free formulations of tafluprost showed a similar IOP-lowering effect of 5 to 6 mmHg at Week 4. Both the preservative-free and preservative-containing formulations were generally well-tolerated.

Table 8 - IOP by Visit and Time Point (Protocol 77550)

Visit	Time Point	Tafluprost Preserved Formulation			Tafluprost Preservative-free Formulation		
		N[a]	Mean (SD) mmHg	Change (% Change)[b]	N[a]	Mean (SD) mmHg	Change (% Change)[b]
Baseline	8:00	42	22.6 (3.0)	--	43	23.0 (3.2)	--
	12:00	42	20.9 (2.8)	--	43	21.8 (2.7)	--
	16:00	42	21.7 (3.2)	--	43	21.5 (2.5)	--
	20:00	42	21.8 (3.0)	--	43	21.8 (2.6)	--
Week 1	8:00	42	16.4 (2.1)	-6.1 (-26.2)	43	16.2 (2.7)	-6.8 (-28.9)
	12:00	42	15.8 (1.6)	-5.1 (-23.3)	43	15.7 (1.9)	-6.1 (-27.3)
	16:00	42	16.2 (1.7)	-5.5 (-23.4)	43	15.8 (2.0)	-5.7 (-25.8)
	20:00	42	16.3 (2.2)	-5.5 (-24.8)	43	16.2 (2.1)	-5.7 (-25.2)
Week 4	8:00	42	16.4 (2.4)	-6.2 (-26.6)	43	16.8 (3.0)	-6.2 (-26.6)
	12:00	42	16.3 (2.5)	-4.6 (-21.0)	43	16.7 (2.5)	-5.1 (-23.1)
	16:00	42	16.6 (2.4)	-5.1 (-22.3)	43	16.7 (2.5)	-4.8 (-21.6)
	20:00	42	17.2 (1.9)	-4.6 (-19.9)	43	17.0 (2.4)	-4.8 (-21.3)

a. N = Number of patients included in the analysis at the corresponding visit and time point.

b. Mean absolute change (mmHg) and percentage change (%) from baseline.

Analysis details: Intention-to-treat population; Repeated measurements analysis of covariance; Worse eye.

Open-label Preservative-free Crossover Study (Protocol 77552)

The tolerability and IOP-reducing effect of preservative-free tafluprost was investigated in an open-label, phase IIIb study of 158 patients exhibiting ocular surface signs or symptoms during latanoprost 0.005% treatment. Preservative-free tafluprost 0.0015% maintained IOP at the same level after 12 weeks treatment as latanoprost at baseline. After switching to tafluprost, the number of patients with abnormal Schirmer's test was significantly reduced, and, tear break-up time improved significantly. A reduction in the number of patients with abnormal conjunctival cells based on HLA-DR and MUC5AC was also detected. Patients had fewer ocular signs or symptoms while taking preservative-free tafluprost than while taking latanoprost.

Table 9 - Mean IOP of the Treated Eyes during the Study

	Baseline (N=158) Mean (SD)	2 weeks (N=157) Mean (SD)	6 weeks (N=156) Mean (SD)	12 weeks (N=155) Mean (SD)
IOP (mmHg)	16.77 (2.52)	16.23 (2.42)	16.36 (2.52)	16.44 (2.69)

Table 10 - Tear Secretion/Schirmer Test at Baseline, Week 6 and Week 12

	Baseline (N=158) Mean (SD)	Week 6 (N=156) Mean (SD)	Week 12 (N=155) Mean (SD)
Tear secretion/Schirmer test (mm)	9.6 (8.17)	10.9 (9.54)	10.5 (8.97)

Table 11 - Tear Break-Up Time (tBUT) at Baseline, Week 6 and Week 12

	Baseline (N=158) Mean (SD)	Week 6 (N=156) Mean (SD)	Week 12 (N=155) Mean (SD)
Tear break-up time (seconds)	4.5 (2.49)	6.7 (4.31)	7.8 (4.86)

Table 12 - Number (percentage) of Patients With Abnormal Levels of HLA-DR-Positive Epithelial Cells at Baseline, Week 6 and Week 12

	Abnormal[a] at Baseline (N=152)	Abnormal[a] at 6 weeks (N=151)	Abnormal[a] at 12 weeks (N=152)
HLA-DR-positive epithelial cells	100 (65.8%)	68 (45.0%)	87 (57.2%)

a. ≥ 40% of HLA-DR positive cells

Table 13 - Number (percentage) of Patients with Abnormal Levels of MUC5AC-Expressing Goblet Cells at Baseline, Week 6 and Week 12

	Abnormal[a] at Baseline (N=142)	Abnormal[a] at 6 weeks (N=146)	Abnormal[a] at 12 weeks (N=150)
MUC5AC-expressing goblet cells	99 (69.7%)	75 (51.4%)	77 (51.3%)

a. < 7% of cells positive to the mucin marker, related to MUC5AC-expressing cells

Table 14 - Number (Percentage) of Patients with Abnormal Ocular Signs at Baseline, Week 6 and Week 12

Ocular Sign (worse eye)	Abnormal[a] at Baseline (N=158)	Abnormal[a] at 6 weeks (N=156)	Abnormal[a] at 12 weeks (N=155)
Tear break-up time (tBUT)	150 (94.9%)	120 (76.9%)	111 (71.6%)
Corneal fluorescein staining	129 (81.6%)	82 (52.6%)	63 (40.6%)
Conjunctival fluorescein staining	133 (84.2%)	84 (53.8%)	67 (43.2%)
Blepharitis	95 (60.1%)	66 (42.3%)	63 (40.6%)
Conjunctival redness/hyperemia	133 (84.2%)	108 (69.2%)	93 (60.0%)
Tear secretion/Schirmer test	113 (71.5%)	96 (61.5%)[b]	92 (59.4%)[b]

a. tBUT < 10 sec; At least grade I corneal staining; At least grade II combined (nasal and temporal) conjunctival staining; At least mild blepharitis; At least mild conjunctival redness; Schirmer test value 10 mm or less.

b. p=0.014 at 6 weeks and p=0.003 at 12 weeks for tear secretion (from McNemar's test for changes from baseline in proportions). For all other signs at both visits, the p-values were < 0.001.

Table 15 - Number (Percentage) of Patients with Abnormal Ocular Symptoms at Baseline, Week 6 and Week 12

Ocular Symptom	Abnormal[a] at Baseline (N=158)	Abnormal[a] at 6 weeks (N=156)	Abnormal[a] at 12 weeks (N=155)
Irritation/burning/stinging	89 (56.3%)	48 (30.8%)	44 (28.4%)
Foreign body sensation	78 (49.4%)	45 (28.8%)	42 (27.1%)
Tearing	87 (55.1%)	40 (25.6%)	42 (27.1%)
Itching	74 (46.8%)	40 (25.6%)	41 (26.5%)
Dry eye sensation	102 (64.6%)	55 (35.3%)	61 (39.4%)

a. At least mild severity grading.

13 NON-CLINICAL TOXICOLOGY

Animal Pharmacology

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

Chronic Toxicity

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.

Carcinogenicity
Tafluprost was not carcinogenic when administered subcutaneously daily for 24 months at doses up to 30 mcg/kg/day in rats and for 18 months at doses up to 100 mcg/kg/day in mice (over 1600- and 1300-times, respectively, the maximum clinical exposure based on plasma AUC).

Mutagenesis
Tafluprost was not mutagenic or clastogenic in a battery of genetic toxicology studies, including an in vitro microbial mutagenesis assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung cells, and an *in vivo* mouse micronucleus assay in bone marrow.

Reproduction
In rats, no adverse effects on mating performance, fertility or early embryonic development were observed with intravenous dosing of tafluprost at systemic exposure over 14000-times the maximum clinical exposure based on C_{max} or greater than 3600-times based on AUC.

Development
In embryo-fetal development studies in rats and rabbits, tafluprost administered intravenously caused increases in post-implantation losses in rats and rabbits and reductions in fetal body weights in rats. Tafluprost also increased the incidence of vertebral skeletal abnormalities in rats and the incidence of skull, brain and spine malformations in rabbits. In rats, there were no adverse effects on embryo-fetal development at a dose of 3 mcg/kg/day corresponding to maternal plasma levels of tafluprost acid that were 343-times the maximum clinical exposure based on C_{max}. In rabbits, effects were seen at tafluprost dose of 0.03 mcg/kg/day corresponding to maternal plasma levels of tafluprost acid during the critical period of development that were 5.3-times higher than the clinical exposure based on C_{max}. At the no effect dose in rabbits (0.01 mcg/kg/day), maternal plasma levels of tafluprost acid were below the lower level of quantification (20 pg/mL).

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 no observed adverse effect level was at a tafluprost intravenous dose of 0.3 mcg/kg/day which is greater than 3 times the maximum recommended clinical dose based on body surface area comparison.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrSAFLUTAN™
Tafluprost Ophthalmic Solution, 15mcg/mL
(Preservative-free)

Read this carefully before you start taking **SAFLUTAN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SAFLUTAN**.

What is SAFLUTAN used for?
SAFLUTAN lowers the pressure in the eye for conditions such as open-angle glaucoma or ocular hypertension.

SAFLUTAN increases the flow of fluid out of the eye thereby reducing eye pressure.

How does SAFLUTAN work?
SAFLUTAN belongs to a group of medicines called prostaglandin analogues. SAFLUTAN increases the flow of fluid out of the eye. This helps lower the pressure in the eye.

What are the ingredients in SAFLUTAN?

Medicinal ingredients:	tafluprost
Non-medicinal ingredients:	disodium edetate, glycerol, polysorbate 80, and sodium dihydrogen phosphate dihydrate. Hydrochloric acid and/or sodium hydroxide are added to adjust the pH. SAFLUTAN is preservative-free. It does not contain the preservative benzalkonium chloride.

SAFLUTAN comes in the following dosage forms:
SAFLUTAN is a clear, colorless liquid (solution) supplied in single-dose plastic containers, each containing 0.3 mL of solution (tafluprost 4.5 mcg). Ten single-dose containers are provided in one foil pouch and 3 pouches are in a carton.

Do not use SAFLUTAN if:
Do not use SAFLUTAN if you are allergic to any of its ingredients. (See What are the ingredients in SAFLUTAN?)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SAFLUTAN. Talk about any health conditions or problems you may have, including if you:
- have any medical problems you have now or have had in the past. This includesany other eye disease.
- have any allergies.
- are breast feeding or intend to breast feed.
- are breast feeding or intend to breast feed.

- are of child-bearing years. You should use an effective form of birth control when taking SAFLUTAN.
- have now or have had in the past liver problems
- have now or have had in the past kidney problems
- have now or have had in the past any lung problems, including asthma.

Other warnings you should know about:
While using SAFLUTAN you may experience the following side effects, some of which may be permanent. These effects may occur slowly and it may be several months before you notice them. SAFLUTAN may:
- increase the length, thickness, color and/or number of your eyelashes. It may cause unusual hair growth on your eyelids.
- cause darkening of the color of the skin around the eyes. Blot off any excess solution from the skin. This will reduce the risk of skin darkening.
- change the color of your iris (the colored part of your eye). If SAFLUTAN is used in one eye only, the color of the treated eye may become different from the color of the other eye. This may be permanent.

You may find that your vision is blurred for a time just after you put SAFLUTAN in your eye. Do not drive or use any tools or machines until your vision is clear.

SAFLUTAN is not recommended for use in children or adolescents below 18 years of age.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

No drug interaction studies have been done for SAFLUTAN. Tell your doctor about all drugs, including other eyedrops, that you are using or plan to use.

How to take SAFLUTAN:
- Always use SAFLUTAN exactly as your doctor has told you.
- You should check with your doctor or pharmacist if you are not sure how to use SAFLUTAN.
- Remove contact lenses before using SAFLUTAN. They can be reinserted 15 minutes after using SAFLUTAN.

Instructions for Use:

When you start a new pouch:

Do not use the single-dose containers if the pouch is broken. Open the pouch along the dashed line. Write down the date you opened the pouch in the space reserved for the date on the pouch.

Every time you use SAFLUTAN:

Step 1 Wash your hands.

Step 2 Take the strip of containers from the pouch.

Step 3 Detach one single-dose container from the strip.

Step 4 Put the remaining strip back in the pouch and fold the edge to close the pouch.

Step 5 Make sure that the solution is in the bottom part of the single-dose container.

Figure A

Step 6 To open the container, twist off the tab.

Figure B

Step 7 Tilt your head backwards. If you are unable to tilt your head, lie down.

Step 8 Place the tip of the container close to your eye. Be careful not to touch the tip of the container to the eye itself.

Figure C

Step 9 Pull the lower eyelid downwards and look up.

Step 10 Gently squeeze the container and let one drop fall into the space between the lower eyelid and the eye.

Figure D

Step 11 Close your eye for a moment and press the inner corner of the eye with your finger for about one minute. This helps to prevent the eye drop from draining down the tear duct.

Step 12 Blot off any excess solution from the skin around the eye with a tissue.

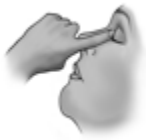


Figure E

If a drop misses your eye, try again.

If your doctor has told you to use drops in both eyes, repeat steps 7 to 12 for your other eye.

The contents of one container of SAFLUTAN are enough for both eyes. Use the solution immediately after opening. **Discard the opened container with any remaining contents immediately after use.**

Usual dose:
The dose is 1 drop of SAFLUTAN in the eye or eyes, once daily in the evening. Only use SAFLUTAN in both eyes if your doctor told you to. Discard the single-use container immediately after use.

Do not instill more drops or use more often than as instructed by your doctor. This may make SAFLUTAN less effective.

If you use other medicines in the eye, leave at least 5 minutes between putting in SAFLUTAN and the other medication.

Do not stop using SAFLUTAN without asking your doctor. If you stop using SAFLUTAN, the pressure in the eye will increase again. This may cause a permanent injury to your eye.

Overdose:
If you use more SAFLUTAN than you should, contact your doctor, but do not stop taking your medicine.

SAFLUTAN is for use as eye drops only and should not be swallowed. If the medicine is accidentally swallowed, please contact a doctor for advice.

If you think you have taken too much SAFLUTAN, contact a health care practitioner (e.g. doctor), hospital emergency department or the regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
It is important to take SAFLUTAN as prescribed by your doctor. If you forget to use SAFLUTAN, use a single drop as soon as you remember, and then put in your next dose at the usual time. Do not use a double dose to make up for a forgotten dose.

What are possible side effects from using SAFLUTAN?

These are not all the possible side effects you may feel when taking SAFLUTAN. If you experience any side effects not listed here, contact your healthcare professional.

- Eye redness
- Itchy eyes
- Eye pain
- Tired eyes
- Burning or stinging eyes
- Dryness and irritation of the eye
- Feeling of something in the eye
- Sensitivity to light
- Change in eyelash colour, thickness, or growth
- Eye or eyelid swelling
- Red, puffy, or itchy eyelid
- Hair growth on the eyelids
- Watery eye
- Eye discharge
- Blurred vision
- Reduction in the ability to see details
- Changes to the surface of the eye
- Changes to the colour of the iris (may be permanent). The iris is the coloured part of the eye.
- Changes in the skin colour around the eye.
- Deepening of the eyelid crease (eyes appear sunken)
- Headache
- Dizziness
- Dry mouth
- Cough or sore throat

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN			
Iritis/uveitis (inflammation of the iris or uvea (part of the		√	

eye)): pain and sensitivity to light, possibly with blurred vision.			
Cataract: clouding of the lens in the eye, blurry vision, dim vision and/or eye pain.		√	
Corneal erosion (damage to the front layer of the eyeball): eye redness, pain, tears, burry vision, and feeling of something in the eye.		√	
retinal detachment (separation of the back part of the eye): seeing flashing light or floating spots in the vision, blurry or decreased vision.			√
Worsening of asthma, shortness of breath.		√	
Anaphylactic shock (Allergic Reaction): rash, hives, swelling of the mouth, throat, and lips, difficulty breathing, blue skin, shock, loss of consciousness, low blood pressure.			√

This is not a complete list of side effects. For any unexpected effects while taking SAFLUTAN, contact your doctor or pharmacist.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store the unopened foil pouches of SAFLUTAN in a refrigerator (2°C - 8°C).
- Do not open the pouch until you are about to start using the eye drops.

- Keep out of the sight and reach of children.

After opening the foil pouch:
- Keep the single-dose containers in the original foil pouch.
- Do not store above 25°C.
- Discard any unused single-dose containers after 28 days from date of first opening of the foil pouch.
- Discard an opened single-dose container with any remaining solution immediately after use.

Do not use this medicine after the expiry date stated on the single-dose container, pouch and the outer carton after 'EXP'. The expiry date refers to the last day of that month.

If you want more information about SAFLUTAN:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website http://www.purdue.ca, or by calling 1-800-837-4501.

This leaflet was prepared by Purdue Pharma.

Last Revised: July 29, 2020

Saflutan™ is a trademark of Purdue Pharma.