

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZIOPTAN (tafluprost ophthalmic solution) 0.0015% safely and effectively. See full prescribing information for ZIOPTAN.

ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015%
Initial U.S. Approval: 2012

-----**INDICATIONS AND USAGE**-----

- ZIOPTAN (tafluprost ophthalmic solution) 0.0015% is a prostaglandin analog indicated for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

-----**DOSAGE AND ADMINISTRATION**-----

- One drop in the affected eye(s) once daily in the evening. (2)

-----**DOSAGE FORMS AND STRENGTHS**-----

- Ophthalmic solution containing tafluprost 0.015 mg/mL. (3)

-----**CONTRAINDICATIONS**-----

- None. (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Pigmentation
Pigmentation of the iris, periorbital tissue (eyelid) and eyelashes can occur. Iris pigmentation is likely to be permanent. (5.1)
- Eyelash Changes
Gradual changes to eyelashes including increased length, thickness and number of lashes. Usually reversible. (5.2)

-----**ADVERSE REACTIONS**-----

- Most common ocular adverse reaction is conjunctival hyperemia (range 4% – 20%). (6.1)

To report **SUSPECTED ADVERSE REACTIONS**, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----**USE IN SPECIFIC POPULATIONS**-----

- Use in pediatric patients is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use. (8.4)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling.

Revised: XX/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE**
- 2 DOSAGE AND ADMINISTRATION**
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Pigmentation
 - 5.2 Eyelash Changes
 - 5.3 Intraocular Inflammation
 - 5.4 Macular Edema
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Studies Experience
 - 6.2 Postmarketing Experience
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use

- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES**
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**
 - 17.1 Nightly Application
 - 17.2 Handling the Single-Use Container
 - 17.3 Potential for Pigmentation
 - 17.4 Potential for Eyelash Changes
 - 17.5 When to Seek Physician Advice
 - 17.6 Use with Other Ophthalmic Drugs
 - 17.7 Storage Information

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION**1 INDICATIONS AND USAGE**

ZIOPTAN™ (tafluprost ophthalmic solution) 0.0015% is indicated for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

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

The dose should not exceed once daily since it has been shown that more frequent administration of prostaglandin analogs may lessen the intraocular pressure lowering effect.

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

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

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 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing tafluprost 0.015 mg/mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS**5.1 Pigmentation**

Tafluprost ophthalmic solution 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. 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.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with ZIOPTAN can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly. [See *Patient Counseling Information* (17.3).]

5.2 Eyelash Changes

ZIOPTAN may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, color, thickness, shape and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

ZIOPTAN should be used with caution in patients with active intraocular inflammation (e.g., iritis/uveitis) because the inflammation may be exacerbated.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin F_{2α} analogs. ZIOPTAN should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Preservative-containing or preservative-free tafluprost 0.0015% was evaluated in 905 patients in five controlled clinical studies of up to 24-months duration. The most common adverse reaction observed in patients treated with tafluprost was conjunctival hyperemia which was reported in a range of 4% – 20% of patients. Approximately 1% of patients discontinued therapy due to ocular adverse reactions.

Ocular adverse reactions reported at an incidence of ≥2% in these clinical studies included ocular stinging/irritation (7%), ocular pruritus including allergic conjunctivitis (5%), cataract (3%), dry eye (3%), ocular pain (3%), eyelash darkening (2%), growth of eyelashes (2%) and vision blurred (2%).

Nonocular adverse reactions reported at an incidence of 2% – 6% in these clinical studies in patients treated with tafluprost 0.0015% were headache (6%), common cold (4%), cough (3%) and urinary tract infection (2%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of tafluprost. Because postapproval adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Teratogenic effects: In embryo-fetal development studies in rats and rabbits, tafluprost administered intravenously was teratogenic. Tafluprost 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 µg/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 a tafluprost dose of 0.03 µg/kg/day corresponding to maternal plasma levels of tafluprost acid during organogenesis that were approximately

5 times higher than the clinical exposure based on C_{max} . At the no-effect dose in rabbits (0.01 µg/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 offsprings. The no observed adverse effect level was at a tafluprost intravenous dose of 0.3 µg/kg/day which is greater than 3 times the maximum recommended clinical dose based on body surface area comparison.

There are no adequate and well-controlled studies in pregnant woman. Although animal reproduction studies are not always predictive of human response, ZIOPTAN should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Women of childbearing age/potential should have adequate contraceptive measures in place.

8.3 Nursing Mothers

A study in lactating rats demonstrated that radio-labeled tafluprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZIOPTAN is administered to a nursing woman.

8.4 Pediatric Use

Use in pediatric patients is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

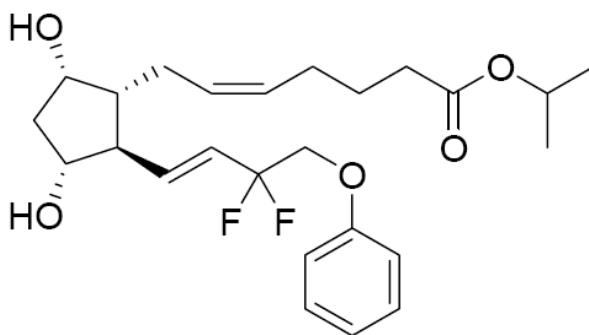
8.5 Geriatric Use

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

11 DESCRIPTION

Tafluprost is a fluorinated analog of prostaglandin F_{2α}. The chemical name for tafluprost is 1-methylethyl (5Z)-7-[(1R, 2R, 3R, 5S)-2-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxycyclopentyl]-5-heptenoate. The molecular formula of tafluprost is C₂₅H₃₄F₂O₅ and its molecular weight is 452.53.

Its structural formula is:



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

ZIOPTAN (tafluprost ophthalmic solution) 0.0015% is supplied as a sterile solution of tafluprost with a pH range of 5.5 - 6.7 and an Osmolality range of 260 – 300 mOsmol/kg.

ZIOPTAN contains Active: tafluprost 0.015 mg/mL; Inactives: glycerol, sodium dihydrogen phosphate dihydrate, disodium edetate, polysorbate 80, hydrochloric acid and/or sodium hydroxide (to adjust pH) and Water for Injection.

ZIOPTAN does not contain a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tafluprost acid, a prostaglandin analog is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

12.3 Pharmacokinetics

Absorption

Following instillation, tafluprost is absorbed through the cornea and is hydrolyzed to the biologically active acid metabolite, tafluprost acid. Following instillation of one drop of the 0.0015% solution once daily into each eye of healthy volunteers, the plasma concentrations of tafluprost acid peaked at a median time of 10 minutes on both Days 1 and 8. The mean plasma C_{max} of tafluprost acid were 26 pg/mL and 27 pg/mL on Day 1, and Day 8, respectively. The mean plasma AUC estimates of tafluprost acid were 394 pg*min/mL and 432 pg*min/mL on Day 1 and 8, respectively.

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.

Elimination

Mean plasma tafluprost acid concentrations were below the limit of quantification of the bioanalytical assay (10 pg/mL) at 30 minutes following topical ocular administration of tafluprost 0.0015% ophthalmic solution.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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.

In rats, no adverse effects on mating performance or fertility were observed with intravenous dosing of tafluprost at a dose of 100 μ g/kg/day (over 14000- times the maximum clinical exposure based on plasma C_{max} or over 3600- times based on plasma AUC).

14 CLINICAL STUDIES

In clinical studies up to 24 months in duration, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 23 - 26 mm Hg who were treated with ZIOPTAN dosed once daily in the evening demonstrated reductions in intraocular pressure at 3 and 6 months of 6 – 8 mmHg and 5 – 8 mmHg, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZIOPTAN (tafluprost ophthalmic solution) 0.0015% is supplied as a sterile solution in translucent low density polyethylene single-use containers packaged in foil pouches (10 single-use containers per pouch). Each single-use container has 0.3 mL solution corresponding to 0.0045 mg tafluprost.

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