DISCLAIMER

All labeling reflected on this website is for informational and promotional purposes only. It is not intended to be used by healthcare professionals or patients for the purpose of prescribing or administering these products. Questions regarding the current content of product labeling should be directed to Akorn's Customer Service department at 800.932.5676.
ZIOPTAN® (tafluprost ophthalmic solution) 0.0015%

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

Dosage and Administration
• One drop in the affected eye(s) once daily in the evening. (2)

DOSE FORMS AND STRENGTHS
• Ophthalmic solution containing tafluprost 0.015 mg/mL. (3)

ADVERSE REACTIONS
Increased intraocular pressure is the most frequently reported adverse event associated with ZIOPTAN®. Reduction of the intraocular pressure starts approximately 2 to 4 hours after the first administration with the maximum effect reached after 12 hours.

Recurrent uveitis may be induced or exacerbated by tafluprost, including iritis, iridocyclitis, iritis/uveitis, and pseudophakic type uveitis. 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.

ADVERSE REACTIONS
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
8.2 Nursing Mothers
8.3 Children
8.4 Pediatric Use
8.5 Geriatric Use

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

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
8.2 Nursing Mothers
8.3 Children
8.4 Pediatric Use
8.5 Geriatric Use

REFERENCES
- 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. (1)

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. (3)

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.
acid that were 343 times the maximum clinical exposure based on \( C_{\text{max}} \). In rabbits, effects were seen at a tafluprost dose of 0.03 mcg/kg/day corresponding to maternal plasma levels of tafluprost acid during organogenesis that were approximately 5 times higher than the clinical exposure based on \( C_{\text{max}} \). 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. 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.

There are no adequate and well-controlled studies in pregnant women. Although animal reproduction studies are not always predictive of human response, ZIOPTAN \(^\circ\) 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 \(^\circ\) 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 F2\(\alpha\). The chemical name for tafluprost is 1-methyl ethyl (5Z,7S)-5-[3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxy cyclo pentyl]-5-heptenoate. The molecular formula of tafluprost is C\(_{22}\)H\(_{24}\)F\(_2\)O\(_7\) and its molecular weight is 452.53.

Its structural formula is:

```
\[
\text{HO} - \text{F} - \text{O}
\]
```

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

ZIOPTAN \(^\circ\) (tafluprost ophthalmic solution) 0.0015\% is supplied as a sterile solution of tafluprost with a pH range of 5.5 to 6.7 and an Osmolarity range of 260 to 300 mOsm/kg.

ZIOPTAN \(^\circ\) 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 \(^\circ\) does not contain a preservative.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Tafluprost acid, a prodrug analog is a selective FP prostaglandin receptor agonist which is believed to reduce intraocular pressure by increasing uveal effl ow. 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 \( C_{\text{max}} \) 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\( \cdot \)min/mL and 432 pg\( \cdot \)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 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 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).

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 mcg/kg/day (over 14000 times the maximum clinical exposure based on plasma \( C_{\text{max}} \) 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 to 26 mm Hg who were treated with ZIOPTAN \(^\circ\) dosed once daily in the evening demonstrated reductions in intraocular pressure at 3 and 6 months of 6 to 8 mmHg and 5 to 8 mmHg, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING
ZIOPTAN \(^\circ\) (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.

NDC 17478-609-30; Unit-of-Use Carton of 30.
NDC 17478-609-90; Unit-of-Use Carton of 90.

Storage:
Store refrigerated at 2\° to 8\°C (36\°F to 46\°F). During shipment ZIOPTAN \(^\circ\) may be maintained at temperatures up to 40\°C (104\°F) for a period not exceeding 2 days. Mail-order prescriptions received after two days of the dispensing date noted in the prescribing label should not be used.

Store in the original pouch. After the pouch is opened, the single-use containers may be stored in the opened foil pouch for up to 30 days at room temperature 20\° to 25\°C (68\° to 77\°F). Protect from moisture. Write down the date you open the foil pouch in the space provided on the pouch. Discard any unused containers 30 days after first opening the pouch.

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling (Patient Information).

17.1 Nightly Application
Advise patients to not exceed once daily dosing since more frequent administration may decrease the intraocular pressure lowering effect of ZIOPTAN \(^\circ\).

17.2 Handling the Single-Use Container
Advise patients that ZIOPTAN \(^\circ\) is a sterile solution that does not contain a preservative. 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.

17.3 Potential for Pigmentation
Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Also inform patients about the possibility of eyelid skin darkening, which may be reversible.

17.4 Potential for Eyelash Changes
Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with ZIOPTAN \(^\circ\). These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

17.5 When to Seek Physician Advice
Advise patients if they develop a new ocular condition (e.g., trauma or infection), experience a sudden decrease in visual acuity, have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of ZIOPTAN \(^\circ\).

17.6 Use with Other Ophthalmic Drugs
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

17.7 Storage Information
Instruct patients on proper storage of cartons, unopened foil pouches, and opened foil pouches [See How Supplied/Storage and Handling (16)]. Recommended storage for cartons and unopened foil pouches is to store refrigerated at 2\° to 8\°C (36\°F to 46\°F). After the pouch is opened, the single-use containers may be stored in the opened foil pouch for up to 30 days at room temperature 20\° to 25\°C (68\° to 77\°F). Protect from moisture.