002201

OPHTHALMIC SOLUTION FOR THE TREATMENT OF
GLAUCOMA AND OCULAR HYPERTENSION

TAFLOTAN® ophthalmic solution 0.0015%

(Tafluprost 0.0015%)

Santen

Composition

Taflotan ophthalmic solution 0.0015% is a clear, colorless, sterile aqueous ophthalmic solution. Each mL contains 15μg of tafluprost. It also contains Polysorbate 80, concentrated glycerin, disodium edetate hydrate, sodium dihydrogen phosphate dihydrate, benzalkonium chloride and pH adjuster (sodium hydroxide, hydrochloric acid) as additives. Its pH is 5.7 - 6.3 and its osmolar ratio is 1.0 - 1.1.

Indications

Reduction of intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension.

Dosage and Administration

Instill 1 drop in the affected eye(s) once daily.

<Precautions>

Do not use more than once daily because more frequent administration may lessen the IOP-lowering effect.

Pharmacology

1.Intraocular pressure (IOP) lowering effect

Ocular administration of tafluprost ophthalmic solutions ranged from 0.00002% to 0.005% in a single dose to monkeys showed the IOP lowering effect in a concentration-dependent manner. The effect was statistically significant in the groups of the concentration of 0.0005% and higher, compared with the vehicle group. In a repeated dose study in monkeys of tafluprost ophthalmic solutions ranged from 0.001% to 0.005% once daily for 5 days, IOP lowering effect at every concentration was stable and did not attenuate during the administration period.

2.Mechanism of action

Tafluprost acid form, an active metabolite, showed high affinity for the prostanoid FP receptor (Ki=0.40 nM). Aqueous humor dynamics in monkeys was evaluated using fluorophotometry, two-level constant pressure perfusion and ^{125}I-^{131}I labelled albumin perfusion methods following the repeated administration of 0.005% tafluprost ophthalmic solution once daily for 3 to 5 days. Uveoscleral outflow significantly increased without any change in aqueous production.

3.Effect on ocular blood flow

(1) A repeated installation of 0.0015% tafluprost ophthalmic solution into rabbit eyes once daily for 28 days significantly increased the blood flow in the optic nerve head, measured with laser speckle method.

(2) A single dose instillation of 0.0015% tafluprost ophthalmic solution into eyes of open-angle glaucoma patients significantly increased the blood flow rate in the optic disc.

Contraindications (This product is contraindicated in the following patients.)

Patients with a history of hypersensitivity to any of the ingredients of this product. Patients with combination with products containing omidenepag isopropyl.

Precautions

1.Careful administration (This product should be administered with care to the following patients.)

1) Patients with aphakia or pseudophakia [this product may induce macular oedema including cystoid macular oedema, and the associated visual acuity reduced.]
2) Patients with bronchial asthma or a history of bronchial asthma [this product may aggravate or induce asthmatic attack.]
3) Patients with endophthalmitis (iritis, uveitis) [other drugs in this category have been reported to cause elevation of intraocular pressure.]
4) Pregnant, parturient and lactating women [see "Use during Pregnancy, Delivery or Lactation".]

2.Important precautions

1) Pigmentation in iris and eyelid (increased melanin content), or hypertrichosis around the eyes may occur. These symptoms gradually progress with continued administration, and stop when the treatment is discontinued. The symptoms like blepharal pigmentation and hypertrichosis around the eyes can gradually disappear or diminish after the administration is discontinued, however, there are reports of cases that symptom of iris pigmentation persists even after the administration was discontinued. In such cases, iris color change can be detected clearly in patient with mixed-colored irises and even in patients with single-color dark brown irises (seen among most Japanese) as well. The difference in iris color between right and left eyes could be noted particularly in the case of unilateral administration. As long-term observation data about these symptoms are not yet available, doctors are required to closely observe patients through periodic checkups. Patients should be well informed of the possibility of these symptoms and instructed to wipe off any excess solution from the skin around the eye or to wash the face in order to prevent blepharal pigmentation or hypertrichosis around the eyes.
2) Corneal epithelium disorder (superficial punctate keratitis, filamentary keratitis or corneal erosion) may occur during treatment. Instruct patients to consult a doctor immediately if subjective symptoms including smarting pain, itching and eye pain, continue.
3) This product should be administered with care because there is no clinical experience in patients with closed angle glaucoma.
4) Temporary blurred vision may develop after administration of this product. Patients should be instructed to refrain from activities like driving or operating machines until the symptom disappears.

3.Adverse Reactions

The following safety data were based on the clinical study result of tafluprost ophthalmic solution 0.0015% containing benzalkonium chloride.

Upon Approval

Adverse drug reactions (including abnormal change in laboratory test values) were reported in 326 of 483 patients (67.5%) in clinical studies in Japan. The major adverse drug reactions were conjunctival hyperaemia in 151 patients (31.3%), abnormality in eyelashes in 93 patients (19.3%), itching in 85 patients (17.6%), eye irritation in 65 patients (13.5%), iris pigmentation in 39 patients (8.1%) etc.

Post-marketing Surveillance

Adverse drug reactions were reported in 396 of 3,260 patients (12.1%) in post-marketing surveillance in Japan. The major adverse drug reactions were blepharal pigmentation in 93 patients (2.9%), conjunctival hyperaemia in 74 patients (2.3%), corneal epithelium disorder including corneal erosion in 58 patients (1.8%), hypertrichosis of eyelids in 40 patients (1.2%), abnormality in eyelashes in 39 patients (1.2%), etc.

1) Clinically significant adverse drug reactions

Iris pigmentation (8.1%): Since iris pigmentation may occur, patients should be examined periodically, and administration should be discontinued depending on the clinical status when iris pigmentation is observed.

2) Other adverse drug reactions

If an adverse drug reaction is observed, appropriate measures including discontinuing administration should be taken.

Type \ Incidence	Incidence unknown	≥5%	5%> ≥1%	1%> ≥0.1%
Ophthalmic	Conjunctivitis, iritis, keratoconjunctivitis sicca, deepening of upper eyelid sulcus, macular oedema	Conjunctival hyperaemia, abnormality in eyelashes (increased length, thickness and number of lashes, etc.), itching, irritation, foreign body sensation, blepharal pigmentation, corneal epithelium disorder including superficial punctate keratitis, abnormal sensation in the eye (discomfort, sticky sensation, dry sensation, etc.)	Eye pain, hypertrichosis of eyelid, eye discharge, photophobia, heavy feeling of eye, lacrimation, blurred vision, conjunctival oedema, blepharitis (redness of eyelid, oedema, etc.)	Subconjunctival hemorrhage
Neuropsychiatric	–	–	Headache	Dizziness
Hypersensitivity	Eyelid dermatitis, rashes	–	Erythema	–
Others	–	–	Elevated AST(GOT), positive urine protein, elevated serum potassium	Elevated ALT(GPT), elevated γ-GTP, positive urine sugar, increased eosinophils, decreased leukocyte count, increased uric acid

Incidence was calculated based on the clinical study results up to the approval of tafluprost ophthalmic solution 0.0015% containing benzalkonium chloride.

4.Use in the elderly

Because physiological function is generally reduced in the elderly, caution should be exercised.

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Approved 16-Sep-2021 05-41 UTC

5.Use during Pregnancy, Delivery or Lactation

1) This product should be used in pregnant women or women who may possibly be pregnant only if the expected therapeutic benefits are judged to outweigh the possible risks associated with the treatment. [The safety of this product for use during pregnancy has not been established. In animal studies, when tafluprost solution was administered intravenously to pregnant rats at a dose of 30μg/kg/day (2000 times the clinical dose*), teratogenicity and post-implantation embryonic mortality rate increased; at 10μg/kg/day (about 670 times the clinical dose*) adverse effect on fetal development (low body weight and unossification of breast bone in fetuses) was observed. In an intravenous administration in pregnant rabbits at 0.1μg/kg/day (about 6.7 times the clinical dose*), miscarriage and mortality rate after implantation increased, and luteal body and implantation decreased; at 0.03μg/kg/day (2 times the clinical dose*) teratogenicity was observed. In an intravenous administration study in pregnant and lactating rats at a dose level of 1μg/kg/day (67 times the clinical dose*), mal-nursing of dams was observed and 4-day survival rate of new born baby decreased. On the other hand, in the study using uteri isolated from rats, uterine contraction was observed at about 3.3 times the plasma concentration of tafluprost (less than 30 pg/mL), or about 420 times the plasma concentration of unbound tafluprost (less than 0.24 pg/mL), calculated based on protein binding ratio, estimated after ocular administration of the clinical dose.]

* Dosage (0.015μg/kg/day) when one drop (30μL) of this product is instilled into both eyes at a time for a 60 kg patient.

2) Avoid administration to nursing mothers. If administration is judged to be essential, the patients should be instructed to stop breast-feeding during the treatment. [A study in rats has shown excretion of tafluprost in breast milk after ocular instillation.]

6.Pediatric Use

The safety of this product to low birth weight infants, neonates, infants or children has not been established. (No clinical experience.)

7.Precautions concerning Use

1) Route of administration: For ophthalmic use only.
2) At the time of administration:
   The following should be instructed to patients.
   (1) Be careful not to touch the tip of the bottle to the eye directly in order to avoid the contamination of the drug.
   (2) Wipe off or wash the face immediately when any excess solution touches the skin around the eye.
   (3) When more than one ophthalmic drug is used, at least 5 minutes of intervals should be taken.
   (4) Contact lenses should be removed prior to administration as benzalkonium chloride contained may cause discoloration of the lenses. Wait for at least 15 minutes before wearing the contact lenses again.

8.Interaction with Other Medicinal Products and Other Forms of Interactions

Contraindication for concomitant use (not to use as concomitant drug).

Name of drugs	Clinical symptom/Action	Mechanism/ Risk factor
Omidenepag isopropyl	Eye inflammation with more than moderate photophobia and iritis etc. be seen with high frequency	Unknown

Clinical Studies

1.In a randomized blind comparative study in 109 patients with primary open angle glaucoma or ocular hypertension using latanoprost ophthalmic solution as a comparator, the decrease in intraocular pressure (IOP) for 0.0015% tafluprost ophthalmic solution was 6.6 mmHg (95% confidence interval: 5.8-7.3 mmHg), which demonstrated non inferiority to the comparator.

Comparison of IOP (mmHg)

	Tafluprost (n=46)	Latanoprost (n=51)
Baseline IOP	23.8±2.3	23.7±2.3
Endpoint IOP (at 4-week or discontinued point)	17.2±2.8	17.5±2.7
Change in IOP	-6.6±2.5	-6.2±2.5
Difference of IOP change (Tafluprost minus comparator)	-0.41	
95% confidence interval of difference of IOP change	-1.42 to 0.60	

(mean ± standard deviation), Non inferiority margin: 2 mmHg

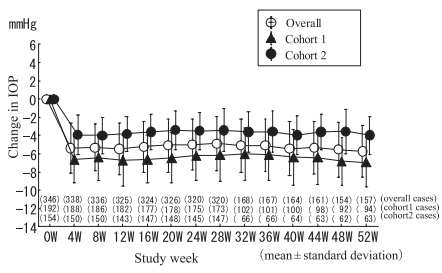
2.In a randomized blind comparative study in 94 patients with normal tension glaucoma using placebo ophthalmic solution as a comparator, the decrease in IOP for 0.0015% tafluprost ophthalmic solution was 4.0 mmHg (95% confidence interval: 3.5-4.5 mmHg), which showed significant IOP lowering effect compared with placebo.

Comparison of IOP (mmHg)

	Tafluprost (n=48)	Placebo (n=42)
Baseline IOP	17.7±1.3	17.8±1.5
Endpoint IOP (at 4-week or discontinued point)	13.8±2.1	16.4±2.2
Change in IOP	-4.0±1.7	-1.4±1.8
Difference of IOP change (Tafluprost minus placebo)	-2.60	
95% confidence interval of difference of IOP change	-3.35 to -1.85	
P value (t-test)	<0.001	

(mean ± standard deviation)

3.In a long-term administration study in 351 patients with open angle glaucoma including normal tension glaucoma, or patients with ocular hypertension, the decrease in IOP for 0.0015% tafluprost ophthalmic solution remained between 4.9 and 5.7 mmHg for 52 weeks, which demonstrated stable IOP lowering effect in a long-term administration. IOP decrease was 6.0-6.9 mmHg in cohort 1* and 3.4-4.0 mmHg in cohort 2 over 52 weeks.



* Cohort 1: 22-34 mmHg at baseline
  Cohort 2: 16-21 mmHg at baseline

4.Reference studies with a tafluprost formulation have demonstrated that tafluprost is effective as monotherapy and has an 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 timepoints 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 24 and 12 months, respectively. 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.

Storage

Store at or below 30˚C. Discard contents one month after opening.

How Supplied

Plastic bottle of 2.5 mL

Manufactured by
SANTEN PHARMACEUTICAL CO., LTD.
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TP-SIN

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06