OPHTHALMIC SOLUTION FOR THE TREATMENT OF
GLAUCOMA AND OCULAR HYPERTENSION

TAFLOTAN® ophthalmic solution

(Tafluprost 0.0015 %)

Santen

Special warning and special precaution for use:
Benzalkonium chloride, which is commonly used as a preservative in ophthalmic product, has been reported to have cytotoxicity. Since this product contains benzalkonium choloride, close monitoring is required with frequent or prolonged use in dry eye patients, or in conditions where the cornea is compromised.
Contact lenses:
The preservative in this product, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses should be instructed to wait at least ten minutes after instilling this product before they insert their contact lenses.

[Composition]

TAFLOTAN® ophthalmic solution 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 as additives. Its pH is 5.7 - 6.3 and its osmolar ratio is 1.0 - 1.1.

[Indications]

Reduction of elevated intraocular pressure in open angle glaucoma and 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 instillation 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 healthy adults significantly increased the blood flow rate in the paraoptic nerve head retinal artery and the blood flow at the paraoptic nerve head retina.

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

Patients with a history of hypersensitivity to any of the ingredients of this product.

[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 stops when the treatment is discontinued. The symptoms like eyelid pigmentation and hypertrichosis around the eyes can gradually fade away or diminish after the administration is discontinued, however, there are reports of cases that symptom of iris pigmentation lingers even after the administration is discontinued. In such cases, iris color change can be detected clearly in patients 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 eyelid pigmentation or hypertrichosis around the eye.
2) Corneal epithelium disorder (superficial punctate keratitis, filamentary keratitis or corneal erosion) may occur during the treatment. Instruct patients to consult a doctor immediately if subjective symptoms including smarting pain, itching or 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

Adverse drug reactions (including abnormal change in laboratory test values) were reported in 326 of 483 patients (67.5%). The major adverse 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%), and iris pigmentation in 39 patients (8.1%), etc.

1) **Clinically significant adverse reaction**
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 reactions**
If an adverse drug reaction is observed, appropriate measures such as discontinuing administration should be taken.

	Incidence unknown	≥5%	5%> ≥1%	1%> ≥0.1%
Ophthalmic	Conjunctivitis, iritis, kerato conjunctivitis 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 epithelial disorder including superficial punctate keratitis, abnormal sensation in the eye (discomfort, sticky sensation, etc.)	Eye pain, hypertrichosis of eyelid, redness of eyelid, eye discharge, photophobia, eyelid oedema, heavy feeling of eye, lacrimation, blurred vision, conjunctival oedema	Subconjunctival hemorrhage
Neuropsychiatric	–	–	Headache	Dizziness

Approved 14-May-2020 06-07 UTC

	Incidence unknown	≥5%	5%> ≥1%	1%> ≥0.1%
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

4.Use in the elderly

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

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 doses 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 of 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 (about 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 dosage.]

* 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:

(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 at least 15 minutes before wearing the contact lenses again.

[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 this product 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 this product was 4.0 mmHg (95% confidence interval : 3.5 - 4.5 mmHg), which showed significant IOP lowering effect compared with placebo.

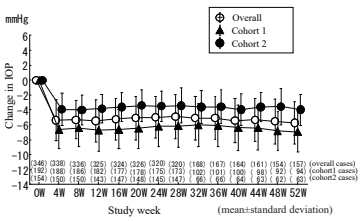
Comparison of IOP (mmHg)

	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 comparator)	-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 this product remained between 4.9 and 5.7 mmHg for 52 weeks, which demonstrated stable IOP lowering effect in 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



[Storage]

Store below 30°C.
After opening, use within 4 weeks.

[Shelf life]

3 years

[How Supplied]

Box of one bottle of 2.5 mL

HARUS DENGAN RESEP DOKTER

Reg. No. DKI1867600946A1

Manufactured by
SANTEN PHARMACEUTICAL CO., LTD.
Shiga plant, Japan

Released by
SANTEN PHARMACEUTICAL CO., LTD.
Noto plant, Ishikawa, Japan

Imported, secondary packaged and marketed by

(print code)

meiji
PT MEIJI INDONESIAN PHARMACEUTICAL INDUSTRIES
Bangil-Pasuruan, Jawa Timur-Indonesia

Approved 14-May-2020 06-07 UTC

Leaflet Taflotan
Date : March 26, 2019
Note :
1. Dimension : 110 x 254 mm
2. Material : HVS 60 g
3. Colour : Black

Page 1

Santen

INFORMASI OBAT UNTUK PASIEN

1. **Nama Obat**
   TAFLOTAN®

2. **Bentuk Sediaan**
   Tetes mata

3. **Pemerian Obat**
   Jernih, tidak berwarna, larutan steril, cairan untuk mata.

4. **Apa yang terkandung dalam obat**
   - Bahan Aktif :
     Setiap ml mengandung 15 µg Tafluprost.
     Setiap botol (2,5 mL) mengandung 37,5 µg Tafluprost.
   - Bahan tambahan : Polysorbate 80, concentrated glycerin, disodium edetate hydrate, sodium dihydrogen phosphate dihydrate, benzalkonium chloride, pengatur pH dan purified water.

5. **Kekuatan zat aktif**
   0,0015%

6. **Untuk apa obat digunakan**
   Taflotan digunakan untuk pengurangan tekanan tinggi intraokular pada glaukoma sudut terbuka dan hipertensi okular.

7. **Berapa banyak dan seberapa sering obat ini boleh digunakan**
   Satu tetes dalam satu hari pada mata yang diobati. Jangan menggunakan lebih dari satu kali sehari karena penggunaan berlebihan dapat mengurangi efek penurunan tekanan tinggi intraokular.
   Jangan hentikan penggunaan obat ini kecuali atas petunjuk dokter.

8. **Pada keadaan apa anda tidak boleh menggunakan obat ini**
   Pasien dengan riwayat hipersensitivitas terhadap salah satu bahan dari produk ini.

9. **Apa yang perlu diperhatikan bila menggunakan obat ini**
   Perhatian dan peringatan khusus penggunaan:
   Benzalkonium chloride, yang biasanya digunakan sebagai pengawet dalam produk tetes mata, telah dilaporkan memiliki efek sitotoksik. Dikarenakan produk ini mengandung benzalkonium chloride, pengawasan yang ketat harus dilakukan dengan berkala atau pada penggunaan jangka panjang pasien dengan mata kering, atau pada kondisi dimana beresiko pada kornea.

   Lensa kontak:
   Pengawet di dalam produk ini, benzalkonium chloride, dapat diabsorbsi oleh lensa kontak. Pasien yang menggunakan lensa kontak harus diinstruksikan agar dapat menunggu setidaknya 10 menit setelah penggunaan produk sebelum mereka menggunakan lensa kontak.

   - *Hal yang harus anda lakukan*
     - Gunakan obat sesuai dengan arahan dokter.
     - Konsultasikan dengan dokter anda jika anda memiliki pertanyaan terkait pengobatan.
     - Informasikan pada dokter anda jika anda merasakan efek samping. Termasuk juga efek lain yang tidak tercantum.
   - *Hal yang tidak boleh anda lakukan*
     Jangan memberikan obat anda kepada orang lain, walaupun mereka memiliki kondisi yang sama dengan anda. Penggunaan Taflotan mungkin tidak aman untuk orang lain. Jangan menghentikan penggunaan Taflotan atau mengubah dosis tanpa resep dokter.
   - *Hal yang perlu diperhatikan*
     Obat ini dapat menyebabkan penglihatan kabur sementara saat digunakan. Jangan mengoperasikan mesin atau mengendarai kendaraan sampai gejala telah sembuh.

10. **Efek samping**
    Efek samping yang paling banyak dilaporkan adalah mata merah, perubahan pada bulu mata (meningkatkan panjang, ketebalan dan jumlah bulu mata), mata gatal/menyengat, pigmentasi kelopak mata (gelap di sekitar mata), gangguan epitel kornea (sakit mata, gangguan fokus, sensasi seperti ada benda asing di mata), dan hipertrikosis kelopak mata. Jika terjadi gejala-gejala tersebut, konsultasikan dengan dokter atau apoteker.
    Gejala yang jarang terjadi adalah perubahan warna iris [iris pigmentasi].
    Jika gejala tersebut terjadi, hentikan pemakaian obat dan segera kunjungi dokter.

11. **Obat dan makanan lainnya yang harus dihindari jika menggunakan obat ini**
    Pastikan dokter dan apoteker mengetahui jika anda sedang menggunakan obat-obatan lain. (Beberapa obat-obatan dapat berinteraksi untuk meningkatkan atau mengurangi efek pengobatan. Berhati-hati terhadap obat yang dijual bebas dan suplemen diet dan juga obat lain yang diresepkan).

12. **Yang harus dilakukan jika kelupaan minum obat**
    Jika anda lupa menggunakan obat, teteskan satu kali sesegera mungkin di hari yang sama. Jika anda baru teringat di hari berikutnya, lewati dosis yang terlupa dan lanjutkan jadwal pengobatan. Anda tidak disarankan meneteskan dua kali dalam sehari atau 2 tetes pada satu pemakaian.

13. Kehamilan dan Menyusui
Pastikan untuk memberitahu ke dokter dan apoteker anda.
1. Produk ini dapat digunakan pada wanita hamil jika manfaat terapeutik yang diharapkan yang dinilai lebih besar daripada risiko.
2. Hindari penggunaan pada ibu menyusui. Jika digunakan pada ibu menyusui, pasien harus berhenti menyusui.

14. Efek pada pengendara dan menjalankan mesin
Tidak ada informasi

15. Cara Penyimpanan Obat
- *Cara penyimpanan*
  Jauhkan dari jangkauan anak-anak.
  Simpan pada suhu di bawah 30°C.
  Gunakan selama 4 minggu setelah kemasan dibuka.
- *Pembuangan*
  Tanyakan pada apotek atau institusi medis cara membuangnya

16. Overdosis
Jika anda secara tidak sengaja meneteskan lebih dari yang diresepkan, konsultasikan dengan dokter atau apoteker anda.

17. Nomor Izin Edar
DKI1867600946A1

18. Nama Produsen/ Importir/ Lisensi Produk
Nama produsen
Diproduksi oleh :
SANTEN PHARMACEUTICAL CO., LTD.
Shiga Plant
348-3, Aza-suwa, Oaza-shide, Taga-cho, Inukami-gun, Shiga, Japan

Dirilis oleh :
SANTEN PHARMACEUTICAL CO., LTD.
Noto Plant
2-14, Shikinami, Hodatsushimizu-cho, Hakui-gun, Ishikawa, Japan

Diimpor, dikemas sekunder dan dipasarkan oleh :
meiji **PT MEIJI INDONESIAN PHARMACEUTICAL INDUSTRIES**
Bangil-Pasuruan, Jawa Timur-Indonesia

Nama pemilik produk
SANTEN PHARMACEUTICAL CO., LTD.

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