TRANSPERFECT

I, Marc Adler, hereby declare that (1) I prepare Japanese to English translations for TransPerfect (a translation services company) and I am qualified to do so, (2) I personally prepared the translation attached as Exhibit 1, and (3) the attached translation is, to the best of my knowledge and belief, a true and accurate translation from Japanese to English of the following document, attached as Exhibit 2: Package Insert for Tapros, *available at* https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/300237_1319756Q1022_1_14.

I declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

MARC ADLER
[Print Name]

[Signature]

3-22-18
[Date]

Exhibit 1

[barcode]

**June 2017 Revision (9th ver., precautions revised)
* February 2017 Revision

Japan Standard Product Classification No.
871319

Prostaglandin $F_{2\alpha}$ Derivative
Glaucoma and Ocular Hypertension Treatment

	Tapros Ophthalmic solution 0.0015%	Tapros Mini Ophthalmic solution 0.0015%
Approval no.	22000AMX02366000	22500AMX00003000
NHI price listing	Dec 2008	May 2013
On sale from	Dec 2008	Dec 2013
International birth date	April 2008	

Powerful drug, prescription drug (CAUTION—Use only by prescription from physician, etc.)
TAPROS® ophthalmic solution 0.0015%
Powerful drug, prescription drug (CAUTION—Use only by prescription from physician, etc.)
TAPROS® Mini ophthalmic solution 0.0015%
TAPROS® ophthalmic solution 0.0015%
TAPROS® Mini ophthalmic solution 0.0015%
Tafluprost ophthalmic solution

[barcode]

Tapros ophthalmic solution 0.0015%
Storage: airtight container, room temperature
Expiration date: on box and label (3 years)

Tapros Mini ophthalmic solution 0.0015%
Storage: airtight container, shade, 2-8°C
Expiration date: on box, foil pouches, and container (3 years)

Warning: See handling precautions

Santen

CONTRAINDICATIONS (not to be administered to the following patients)
Patients with a history of sensitivity to the ingredients in the drug.

COMPOSITION/PROPERTIES

Trade Name	Tapros ophthalmic solution 0.0015%	Tapros Mini ophthalmic solution 0.0015%
Active ingredient	Tafluprost	
Content (in 1 mL)	15 μg	
Additives	Polysorbate 80, concentrated glycerin, disodium edetate hydrate, sodium dihydrogen phosphate, benzalkonium chloride, pH modifier	Polysorbate 80, concentrated glycerin, disodium edetate hydrate, sodium dihydrogen phosphate, pH modifier
pH	5.7–6.3	
Osmotic pressure ratio	1.0–1.1	0.9–1.1
Properties	Colorless, transparent, sterile aqueous eye drop	

[EFFICACY/EFFECTIVENESS]
Glaucoma, ocular hypertension

[DOSAGE METHOD/AMOUNT]
One drop per eye per day.

<DOSAGE METHOD/AMOUNT PRECAUTIONS>
The effect of lowering the intraocular pressure might diminish if administered too frequently, so do not use more than once per day.

***[PRECAUTIONS FOR USE]**
1. Careful Administration (use care when administering to the following patients)
1) Patients suffering from aphakia or having intraocular insertion lenses [there are reports of the drug causing macular edema including cystoid macular edema, as well as low vision caused thereby.]
2) Patients currently suffering from or with a history of bronchial asthma [there is a risk of aggravating or inducing asthma attacks.]
3) Patients with endophthalmitis (iritis, uveitis) [there are reports of similar drugs causing an increase in intraocular pressure.]
4) Women who are pregnant, giving birth, or nursing, etc. [See the "Administration to Women who are Pregnant, Giving Birth, or Nursing, etc." section.]

2. Important Basic Warnings
1) Administration of this drug sometimes causes discoloration due to pigment deposits (increases in melanin) in the iris or the eyelid or increases in hair around the eye. These effects progress gradually as the drug is administered but stop when administration stops. Discoloration of the eyelids and increased hair therearound might disappear or diminish gradually after administration is stopped, but there are reports of the discoloration of the iris not disappearing after administration is stopped. The discoloration of the iris is clearly notable in patients with mixed-color irises but is also notable in patients with dark single-colored irises (common among Japanese people). There is a possibility of a difference between the hues of the irises in the left and right eyes, particularly in cases where the drug is administered only to one eye. There is insufficient long-term data on these symptoms, so it is important to see the patient regularly for observation. When administering the drug, fully brief patients on these symptoms and instruct them to wipe their eyelids and wash their faces thoroughly if any of the solution gets on the skin of the eyelids, etc., during administration, in order to prevent or minimize discoloration of the eyelid and increased hair growth therearound.
2) Corneal epithelial disorders can occur when this drug is administered (superficial punctate keratitis, filamentous keratitis, corneal erosion), so instruct patients to come in for examination immediately if they ever become aware of ongoing symptoms such as numbness, itchiness, eye pain, or the like.
3) Caution is required when administering this drug to patients suffering from closed-angle glaucoma, since such use has never been attempted.
4) Temporarily blurred or misty vision can occur after administration, so warn patients not to operate machinery or drive, etc., until such symptoms disappear.

3. Side-Effects
Results of Tapros ophthalmic solution 0.0015% containing benzalkonium chloride are as follows.
At Approval
Of the total 483 cases, side-effects (including abnormal variation of clinical test values) were found in 326 (67.5%). The main side-effects were conjunctival hyperemia (151, 31.3%), problems with eyelashes (93, 19.3%), itchiness (85, 17.6%), sensation of stimulation of the eye (65, 13.5%), and pigmentation of the iris (8.1%).

Investigation of Specific Use Results (5th Regular Safety Report)
Of the total 3,260 cases, side-effects were found in 396 (12.1%). The main side-effects were pigmentation of the eyelid (93, 2.9%), conjunctival hyperemia (74, 2.3%), corneal erosion and other corneal epithelial disorders (58, 1.8%), excessive hair growth on the eyelids (40, 1.2%), and problems with the eyelashes (39, 1.2%).

1) Serious Side-Effects

Pigmentation of the iris (8.1%): Pigmentation of the iris can occur, so patients need to be seen regularly, and administration should be stopped depending on the clinical state if such pigmentation occurs.

2) Other Side-Effects

Take appropriate steps, including halting administration, if other side-effects occur.

Type \ Freq	Unknown freq.	5% or more	1-5%	1%
Eye	Conjunctivitis, iritis, kerato-conjunctivitis sicca, deepening of the suprapalpebral sulcus, macular edema	Conjunctival hyperemia, problems with the eyelashes (lengthening, thickening of eyelashes or increase in number, etc.) itchiness, sense of stimulation, feeling of something in eye, eyelid pigmentation, superficial punctate keratitis and other corneal epithelial disorders, discomfort in the eyes (strange feeling, stickiness, dryness, etc.)	Eye pain, increased hair on eyelid, discharge, photophobia, heavy feeling, tearing, blurred vision, macular edema, swelling of the eyelid (redness of the eyelid, edema, etc.)	Sub-conjunctival hemorrhage
Neuro-psychiatric	—	—	Headache	Dizziness
Sensitivity	Eyelid swelling	—	Erythema	-
Other			AST (GOT) increase, positive urinary protein, serum potassium increase	ALT (GPT) increase, γ-GTP increase, positive urinary sugar, increase in acidophilic leukocytes, reduction in white blood cell count, uric acid increase

Frequency of presentation was calculated on the basis of clinical trial results up to approval of Tapros ophthalmic solution 0.0015% containing benzalkonium chloride.

4. Administration to the Elderly

Use caution, since physiological functions are generally lowered in the elderly.

5. Administration to Women who are Pregnant, Giving Birth, or Nursing, etc.

1) Only administer this drug to women who are or might be pregnant in cases where the therapeutic benefit is deemed to outweigh the risks. [The safety of administration during pregnancy has not been established. In animal trials, there was an increase in teratogenicity and post-implantation losses after intravenous administration of 30 μg/kg/day (2000 times the clinical dosage) to pregnant rats, and growth of fetuses was affected (low fetal weight and unossifsication of the sternum) at 10 μg/kg/day (approx. 670 times the clinical dosage). An increase in miscarriages, post-implantation losses, lower luteal bodies, and smaller litters were seen after intravenous administration of 0.1 μg/kg/day (approx. 6.7 times the clinical dosage) to pregnant rabbits, and teratogenicity was found at 0.03 μg/kg/day (twice the clinical dosage). Intravenous administration of 1 μg/kg/day (approx. 67 times the clinical dosage) resulted in problems with nursing and a lowering of the day four survival rate of offspring. In tests using extracted rat uteri, shrinkage of the uterus was seen at approx. 3.3 times the estimated plasma concentration (less than 30 pg/mL) during administration of the clinical dosage* as eye drops, or approx. 420 times the estimated plasma unbound drug concentration when converted using the protein binding ratio (less than 0.24 pg/mL).

*The dosage (0.015 μg/kg/day) when a 0.0015% solution of the drug is administered to each eye as one drop (30 μL) per day to a patient weighing 60 kg.

2) Avoid administering the drug to nursing mothers, but if it is necessary, make the mother stop the nursing. [Transmission to the milk has been reported in animal testing (rats: eyedrop administration).]

6. Administration to Children, etc.

The safety of administration to low-birth-weight children, newborns, nursing children, infants, and toddlers has not been established (no data).

7. Caution in Application

1) Administration path: only use as eyedrops.

2) When administering:

Instruct patients to take care with the following.

(1) To prevent contamination of the drug solution, do not allow the tip of the container to come in direct contact with the eye during administration.

(2) If the solution gets on the eyelid skin, etc., wipe off immediately and wash your face.

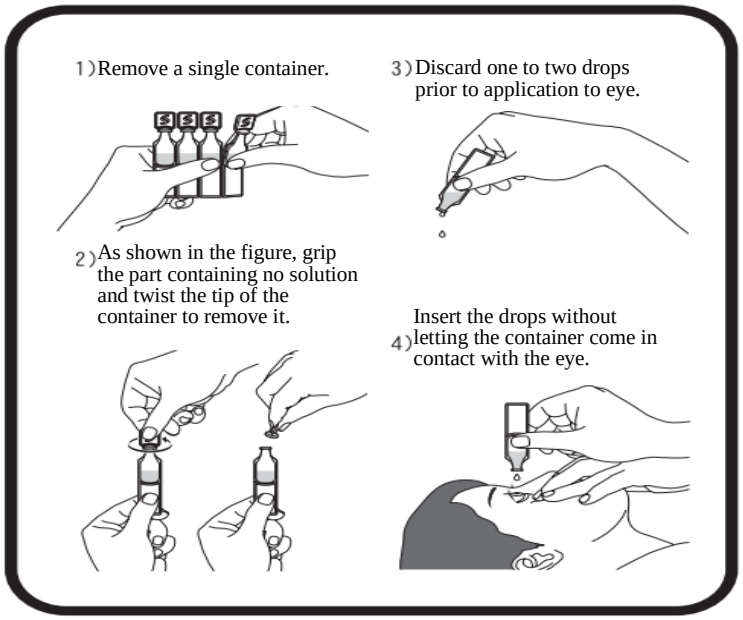
(3) When used in conjunction with other eyedrops, space administration at least five minutes apart.

(4) Benzalkonium chloride can discolor contact lenses, so if this drug is administered when wearing contacts, remove the contacts, apply the drug, and then reinsert the contacts no sooner than 15 minutes later.
(Tapros ophthalmic solution 0.0015% only)

(5) During use, discard the first one or two drops (to remove any pieces of the container after opening).
(Tapros Mini ophthalmic solution 0.0015% only)

(6) Discard any unused solution, since it is a single-use sterile disposable solution which contains no preservatives to prevent secondary contamination.
(Tapros Mini ophthalmic solution 0.0015% only)

How to Administer Tapros Mini Ophthalmic Solution 0.0015%



[PHARMACOKINETICS]

1. Plasma concentration[1)]

When one drop per day was administered for seven days to seven healthy adults each in a 0.0025% or 0.005% Tafluprost ophthalmic solution group, the plasma concentration of Tafluprost or Tafluprost carboxylic acid which is the active metabolite was detected as 0.144 ng/mL of Tafluprost carboxylic acid after 15 min after administration on the first day in one case in the 0.0025% group, but aside from that all measurements were below the lower limits (Tafluprost: 0.2 ng/mL, Tafluprost carboxylic acid: 0.1 ng/mL).
Note: the concentration of the drug is 0.0015%.

2. Transmission in Animal Eye Tissue[2)]

(Reference: monkey)
When a single dose of 0.005%[3] H-Tafluprost ophthalmic solution was administered to a monkey, radiation distributed rapidly throughout the eye tissue, the maximum radiation concentration was seen in the cornea and conjunctiva 5–15 min after administration, and two hours after administration in the aqueous humor, the ciliary body, and the crystalline lens, after which it rapidly disappeared.

[CLINICAL RESULTS]

1. In a randomized blind study of 109 patients suffering from primary open-angle glaucoma or ocular hypertension (control drug: Latanoprost ophthalmic solution), there was a 6.6 mmHg drop in intraocular pressure with Tapros ophthalmic solution 0.0015% (5.8–7.3 mmHg in the 95% confidence interval), verifying noninferiority relative to the control drug.[3)]

Comparison of Intraocular Pressure (mmHg)

	Tapros ophthalmic solution 0.0015% (n=46)	Control drug (n=51)
Baseline	23.8 ± 2.3	23.7 ± 2.3
After treatment period (after four weeks or when ended)	17.2 ± 2.8	17.5 ± 2.7
Change in intraocular pressure	–6.6 ± 2.5	–6.2 ± 2.5
Group difference in average (Tapros ophthalmic solution 0.0015% – control drug)	–0.41	
95% confidence interval for difference in averages	–1.42 to 0.60	

(Average ± standard dev.)
Noninferiority limit: 2 mmHg

2. In a randomized blind study of 94 patients suffering from normal tension glaucoma (control drug: placebo ophthalmic solution), there was a 4.0 mmHg drop in intraocular pressure with Tapros ophthalmic solution 0.0015% (3.5–4.5 mmHg in the 95% confidence interval), demonstrating a significant drop in intraocular pressure compared to the control drug.[4)]

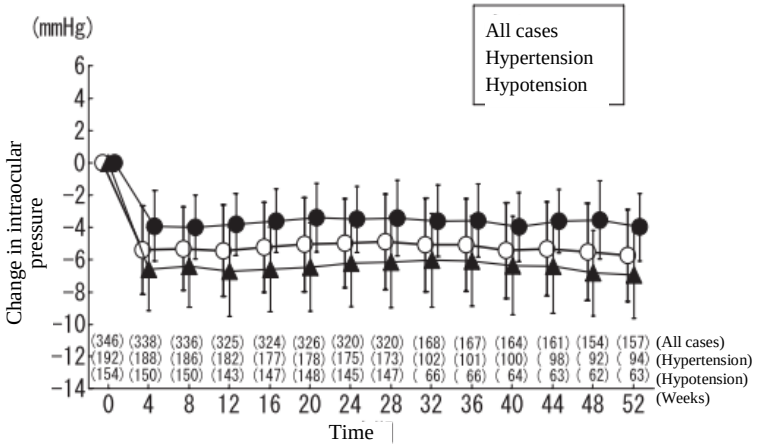
Comparison of Intraocular Pressure (mmHg)

	Tapros ophthalmic solution 0.0015% (n=46)	Control drug (n=51)
Baseline	23.8 ± 2.3	23.7 ± 2.3
After treatment period (after four weeks or when ended)	17.2 ± 2.8	17.5 ± 2.7
Change in intraocular pressure	–6.6 ± 2.5	–6.2 ± 2.5
Group difference in average (Tapros ophthalmic solution 0.0015% – control drug)	–0.41	
95% confidence interval for difference in averages	–1.42 to 0.60	

(Average ± standard dev.)
Noninferiority limit: 2 mmHg

3. In a long-term trial of 351 patients suffering from elevated intraocular pressure or open-angle glaucoma, including normal tension glaucoma, the drop in intraocular pressure from Tapros ophthalmic solution 0.0015% was 4.9–5.7 mmHg for 52 weeks, and the effect of lowering the intraocular pressure was maintained stably in all long-term cases. Of these, the drop in intraocular pressure in the ocular hypertension group* was 6.0–6.9 mmHg for 52 weeks, and 3.4–4.0 mmHg in the hypotension group*.[5)]

*The hypertension group had a baseline intraocular pressure of 22–34 mmHg and the hypotension group had one of 16–21 mmHg.



Average ± standard dev.

[PHARMACOLOGY]

1. Effect of Lowering Intraocular Pressure[6)]

When 0.00002% to 0.005% Tafluprost ophthalmic solution was administered as a single eye drop to monkeys, a concentration-dependent drop in intraocular pressure effect was found which was significant relative to the base drug group at a concentration of 0.0005% or above. When 0.001% to 0.005% Tafluprost ophthalmic solution was administered to monkeys once a day for five days, the drop in intraocular pressure continued stably over the entire period at all dosages, without any weakening of the effect.

2. Mechanism of Action[6)]

Tafluprost carboxylic acid, the active metabolite, displayed affinity (Ki = 0.40 nM) to prostanoid FP receptors. Monkeys were given one dose per day of 0.005% Tafluprost ophthalmic solution for three to five days, and the aqueous humor dynamics were measured using fluorophotometry, two-level constant perfusion, ^{125}I–^{131}I-labeled albumin perfusion. No changes were seen in aqueous humor production, and there was a significant increase in the uvea sclera flow.

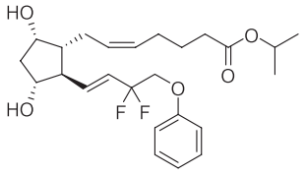
3. Effect on Ocular Blood Flow

1) Tapros ophthalmic solution 0.0015% was administered once a day for 28 days to rabbits, and when measurements were done using a laser speckle method, a significant increase was seen in the blood flow in the papillary tissue of the optic nerve.[7)]

2) When healthy adults were given a single dose of Tapros ophthalmic solution, significant increases were seen in the blood flow velocity in the perioptic papillary retinal artery and the tissue of the perioptic papillary retina.[8)]

[PHYSICOCHEMICAL FINDINGS ON THE ACTIVE INGREDIENT]

Common name: Tafluprost
Chemical name: 1-Methylethyl (5*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-2-[(1*E*)-3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxycyclopentyl}-5-heptenoate
Chemical structure:



Molecular formula: $C_{25}H_{34}F_2O_5$
Molecular weight: 452.53
Properties: Colorless to light-yellow viscous liquid. Dissolves in ethanol, diethylether, and acetonitrile, but is practically insoluble in water.

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