

Reproductive system and breast disorders	Peyronie's disease, decreased libido, sexual dysfunction.
General disorders and administration site conditions	Asthenia/fatigue, thirst.

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose and Treatment

A topical overdose with tafluprost is not likely to occur or to be associated with toxicity.

There have been reports of inadvertent overdosage with timolol resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also section 4.8).

If overdose with Tapcom-S occurs, treatment should be symptomatic and supportive. Timolol does not dialyse readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, beta blocking agents, ATC code: S01ED51

Mechanism of action

Tapcom-S is a fixed combination of two active substances tafluprost and timolol. These two active substances lower intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone.

Tafluprost is a fluorinated analogue of prostaglandin F_{2α}. Tafluprost acid, the biologically active metabolite of tafluprost, is a highly potent and selective agonist of the human prostanoid FP receptor. Pharmacodynamic studies in monkeys indicate that tafluprost reduces intraocular pressure by increasing the uveoscleral outflow of aqueous humour.

Timolol maleate is a non-selective beta-adrenergic receptor blocking agent. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

Clinical efficacy

In a 6-month study (n=400) in patients with open-angle glaucoma or ocular hypertension and mean untreated IOPs between 24-26 mmHg, the IOP lowering effect of Tapcom-S (once daily in the morning) was compared to concomitant administration of 0.0015% tafluprost (once daily in the morning) and 0.5% timolol (twice daily). Tapcom-S was non-inferior to the effect of concomitantly used 0.0015% tafluprost and 0.5% timolol at all time points and visits with the generally used non-inferiority margin of 1.5 mmHg. The mean diurnal IOP decrease from baseline was 8 mmHg in both arms at the primary endpoint of 6 months (decreases ranging between 7 to 9 mmHg in both arms at the different time points during the day over the study visits).

Another 6-month study (n=564) compared Tapcom-S with the respective monotherapies in patients with open-angle glaucoma or ocular hypertension and mean untreated IOPs between 26-27 mmHg. Patients insufficiently controlled either with 0.0015% tafluprost (IOP 20 mmHg or greater on treatment) or 0.5% timolol (IOP 22 mmHg or greater on treatment) were randomized to be treated with Tapcom-S or the same monotherapy. The mean diurnal IOP reduction of Tapcom-S was statistically superior to that of tafluprost given once daily in the morning or timolol given twice daily, at visits 6 weeks, 3 months (primary efficacy endpoint) and 6 months. The mean diurnal IOP decrease from baseline of Tapcom-S at 3 months was 9 mmHg, in comparison to 7 mmHg observed for both monotherapies. IOP decreases with Tapcom-S at the different time points during the day over the visits ranged between 8 to 9 mmHg in the tafluprost monotherapy comparison group and between 7 to 9 mmHg in the timolol monotherapy comparison group.

Combined data from Tapcom-S patients with high baseline IOP of 26 mmHg (mean diurnal) or above in these two pivotal studies (n=168) showed that the mean diurnal reduction in the IOP was 10 mmHg at the primary end point (3 or 6 months) ranging between 9 and 12 mmHg at the different time points during the day.

5.2 Pharmacokinetic properties

Absorption

Plasma concentrations of tafluprost acid and timolol were investigated in healthy volunteers after single and repeated ocular dosing for eight days of Tapcom-S (once daily), 0.0015% tafluprost (once daily) and 0.5% timolol (twice daily). Tafluprost acid plasma concentrations peaked at 10 minutes after dosing and declined below the lower limit of detection (10 pg/ml) before 30 minutes after Tapcom-S dosing. Accumulation of tafluprost acid was negligible and the tafluprost acid mean AUC_(0-jst) (monotherapy: 4.45±2.57 pg·h/ml; Tapcom-S: 3.60±3.70 pg·h/ml) and the mean C_{max} (monotherapy: 23.9±11.8 pg/ml; Tapcom-S: 18.7±11.9 pg/ml) were both slightly lower with Tapcom-S as compared to tafluprost monotherapy on Day 8. Timolol plasma concentrations peaked at median T_{max} values of 15 and 37.5 minutes after Tapcom-S dosing on Days 1 and 8, respectively. The Day 8 timolol mean AUC_(0-last) (monotherapy: 5750±2440 pg·h/ml; Tapcom-S:4560±2980 pg·h/ml) and the mean C_{max} (monotherapy: 1100 ± 550 pg/ml; Tapcom-S: 840 ± 520 pg/ml) were both somewhat lower with Tapcom-S compared to timolol monotherapy. The lower plasma timolol exposure with Tapcom-S appears to be due to once-daily dosing for Tapcom-S versus twice daily dosing with timolol monotherapy.

Tafluprost and timolol are absorbed through the cornea. In rabbits, corneal penetration of tafluprost from Tapcom-S was similar to that of tafluprost monopreparation after a single instillation while the penetration of timolol was slightly less from the Tapcom-S compared to timolol monopreparation. For tafluprost acid, AUC_{4h} was 7.5 ng·h/ml following administration of Tapcom-S and 7.7 ng·h/ml following administration of tafluprost monopreparation. For timolol, AUC_{4h} was 585 ng·h/ml and 737 ng·h/ml following administration of Tapcom-S and timolol monopreparation, respectively. T_{max} for tafluprost acid was 60 minutes for both Tapcom-S and tafluprost monopreparation, while for timolol T_{max} was 60 min for Tapcom-S and 30 min for timolol monopreparation.

Distribution

Tafluprost

In monkeys, there was no specific distribution of radiolabelled tafluprost in the iris-ciliary body or choroid including retinal pigment epithelium, which suggested low affinity for melanin pigment. In a whole body autoradiography study in rats, the highest concentration of radioactivity was observed in the cornea followed by the eyelids, sclera and the iris.

Outside the eye radioactivity was distributed to the lacrimal apparatus, palate, oesophagus and gastrointestinal tract, kidney, liver, gall bladder and urinary bladder. The binding of tafluprost acid to human serum albumin *in vitro* was 99% at 500 ng/ml tafluprost acid.

Timolol

The peak level of timolol-related radioactivity in the aqueous humor was reached after 30 minutes following a single application of 3H-radiolabelled timolol (0.5% solution: 20 µl/eye) to both eyes in rabbits. Timolol is eliminated from the aqueous humor much faster than from the pigmented tissues iris and ciliary body.

Metabolism

Tafluprost

The principal metabolic pathway of tafluprost in human, which was tested *in vitro*, is the hydrolysis to the pharmacologically active metabolite, tafluprost acid, which is further metabolized by glucuronidation or beta-oxidation. Products of beta-oxidation, 1,2-dinor and 1,2,3,4-tetranor tafluprost acids, which are pharmacologically inactive, may be glucuronidated or hydroxylated. Cytochrome P450 (CYP) enzyme system is not involved in the metabolism of tafluprost acid. Based on the study in rabbit corneal tissue and with purified enzymes, the main esterase responsible for the ester hydrolysis to tafluprost acid is carboxyl esterase. Butylcholine esterase but not acetylcholine esterase may also contribute to the hydrolysis.

Timolol

Timolol is metabolized in the liver primarily by CYP2D6 enzyme into inactive metabolites, which are excreted primarily through the kidneys.

Elimination

Tafluprost

Following once daily administration of ³H-tafluprost (0.005% ophthalmic solution; 5 µl/eye) for 21 days to both eyes in rats, approximately 87% of the total radioactive dose was recovered in the excreta. Percent of the total dose excreted in urine was approximately 27-38% and approximately 44-58% of the dose was excreted in the feces.

Timolol

Apparent elimination half-life from the human plasma is about 4 hours. Timolol is extensively metabolised in the liver and the metabolites are excreted in the urine in addition to 20% unchanged timolol following oral administration.

5.3 Preclinical safety data

Tapcom-S

Non-clinical data reveal no special hazard for humans based on repeated dose toxicity study and ocular pharmacokinetic studies. The ocular and systemic safety profile of the individual components is well established.

Tafluprost

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, systemic repeated dose toxicity, genotoxicity and carcinogenic potential. As with other PGF2 agonists, repeated dose topical ocular administration of tafluprost to monkeys produced irreversible effects on iris pigmentation and reversible enlargement of the palpebral fissure.

Increased contraction of rat and rabbit uteri *in vitro* was observed at tafluprost acid concentrations that exceeded 4 to 40 times, respectively, the maximum plasma concentrations of tafluprost acid in humans. Uterotonic activity of tafluprost has not been tested in human uterus preparations.

Reproduction toxicity studies were performed in the rat and rabbit with intravenous administration. In rats, no adverse effects on fertility or early embryonic development were observed at systemic exposure over 12,000 times the maximum clinical exposure based on C_{max} or greater than 2,200 times based on AUC.

In conventional embryo-foetal development studies, tafluprost caused reductions in foetal body weights and increases in post-implantation losses. Tafluprost increased the incidence of skeletal abnormalities in rats as well as the incidence of skull, brain and spine malformations in rabbits. In the rabbit study, plasma levels of tafluprost and its metabolites were below the level of quantification.

In a pre- and postnatal development study in rats, increased mortality of newborns, decreased body weights and delayed pinna unfolding were observed in offspring at tafluprost doses greater than 20 times the clinical dose.

The experiments in rats with radiolabelled tafluprost showed that around 0.1% of the topically applied dose on eyes was transferred into milk. As the half-life of active metabolite (tafluprost acid) in plasma is very short (not detectable after 30 minutes in humans), most of the radioactivity probably represented metabolites with little, or no pharmacologic activity. Based on metabolism of tafluprost and natural prostaglandins, the oral bioavailability is expected to be very low.

Timolol

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Disodium phosphate dodecahydrate Disodium edetate
Polysorbate 80
Hydrochloric acid, concentrated and/or sodium hydroxide for pH adjustment Water for injections.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years
After first opening a foil pouch:28 days.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). After opening the foil pouch:
•Do not store above 25°C and protect from light.
•Use within 28 days .
•Discard an opened single-dose container with any remaining solution immediately after use.

6.5 Nature and contents of container

Low-density polyethylene (LDPE) single-dose containers packed in a foil pouch made of a paper-coated, aluminum-polyethylene laminate. Each single-dose container has a fill volume of 0.3 ml and there are 10 containers in each foil pouch.

The following pack sizes are available: 30 x 0.3 ml single-dose containers.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRATION HOLDER

Santen Pharma Malaysia Sdn. Bhd.
Unit #23A-10, Q Sentral,
No. 2A, Jalan Stesen Sentral 2,

Kuala Lumpur Sentral,
50470 Kuala Lumpur, Malaysia.

8. MANUFACTURED BY

Laboratoire Unither
1 Rue De L Arquerie,
Coutances, 50200
France

9. DATE OF REVISION OF THE TEXT

May 2022

Artwork informations

CAW-2641-03

Tapcom-S MY

Désignation

65NOT7684/F

Unither packaging code

200 x 560 mm

Open size

200 x 280 mm

Folded size

Black

Colours on front side

Black

Colours on back side