TAPCOM®-S Ophthalmic Solution
Tafluprost 15 micrograms/ml and timolol (as maleate) 5 mg/ml

CONTRAINDICATIONS (This product is contraindicated in the following patients.)
Hypersensitivity to the active substances or to any of the excipients listed in PHARMACEUTICAL PARTICULARS, 1. List of excipients.
Reactive airway disease including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
Sinus bradycardia, sick sinus syndrome, including sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.

Patients with combination with products containing omidenepag isopropyl.

DESCRIPTION
1) Pharmaceutical Dosage Form
Eye drops, solution in single-dose container (eye drops)
A clear, colourless solution with a pH of 6.0-6.7 and an osmolality of 290-370 mOsm/kg.

2) Qualitative and quantitative composition
One ml solution contains: tafluprost 15 micrograms and timolol (as maleate) 5 mg.
One single-dose container (0.3 ml) of eye drops, solution, contains 4.5 micrograms of tafluprost and 1.5 mg of timolol.
One drop (about 30 µl) contains about 0.45 micrograms of tafluprost and 0.15 mg of timolol.

INDICATIONS
Reduction of intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to topical monotherapy with beta-blockers or prostaglandin analogues and require a combination therapy, and who would benefit from preservative free eye drops.

DOSAGE AND ADMINISTRATION
Posology
Recommended therapy is one eye drop in the conjunctival sac of the affected eye(s) once daily.
If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.
Tapcom-S is a preservative free sterile solution packaged in a single-dose container. For single use only, one container is sufficient to treat both eyes. Any unused solution should be discarded immediately after use.

PRECAUTIONS
1. Adverse Reactions
In clinical studies, over 484 patients have been treated with Tapcom-S. The most frequently reported treatment-related adverse event was conjunctival/ocular hyperaemia. It occurred in approximately 7% of the patients participating in the clinical studies in Europe, was mild in most cases, and was associated with discontinuation of treatment in 1.2% of patients.

The adverse reactions reported in the clinical studies using Tapcom-S were limited to those earlier reported for either of the single active substances tafluprost or timolol. No new adverse reactions specific for Tapcom-S were observed in the clinical studies. The majority of adverse reactions reported were ocular, mild or moderate in severity and none were serious.

Like other topically applied ophthalmic agents, tafluprost and timolol are absorbed systemically. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic adverse reactions after topical ophthalmic administration is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

The following adverse reactions have been reported with Tapcom-S during clinical trials (within each frequency grouping, adverse reactions are presented in order of decreasing frequency).
The frequency of possible adverse reactions listed below is defined using the following convention:

Very commom	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Not know	Frequency cannot be estimated from the available data

Tapcom-S (Tafluprost/timolol combination)

System Organ Class	Frequency	Adverse Reactions
Nervous system disorders	Uncommon	Headache.
Eye disorders	Common	Conjunctival/ ocular hyperaemia, eye pruritus, eye pain, change of eyelashes (increased length, thickness and number of lashes), eyelash discolouration, eye irritation, foreign body sensation in eyes, blurred vision, photophobia.
	Uncommon	Abnormal sensation in eye, dry eye, ocular discomfort, conjunctivitis, erythema of eyelid, eye allergy, eyelid oedema, superficial punctate keratitis, lacrimation increased, anterior chamber inflammation, asthenopia, blepharitis.

Additional adverse reactions that have been seen with either of the active substances (tafluprost or timolol), and may potentially occur also with Tapcom-S are listed below:

Tafluprost

System Organ Class	Adverse Reactions
Eye disorders	Reduced visual acuity, increased iris pigmentation , blepharal pigmentation, conjunctival oedema, eye discharge, anterior chamber cell, anterior chamber flare, allergic conjunctivitis, conjunctival pigmentation, conjunctival follicles, deepening of eye lid sulcus, iritis/uveitis, macular oedema/ cystoid macular oedema.
Skin and subcutaneous tissue disorders	Hypertrichosis of eyelid.
Respiratory disorders	Exacerbation of asthma, dyspnea.

Timolol

System Organ Class	Adverse Reactions
Immune system disorders	Signs and symptoms of allergic reactions including angioedema, urticaria, localized and generalized rash, anaphylaxis, pruritus.
Metabolism and nutrition disorders	Hypoglycaemia.
Psychiatric disorders	Depression, insomnia, nightmares, memory loss, nervousness, hallucination.
Nervous system disorders	Dizziness, syncope, paraesthesia, increase in signs and symptoms of myasthenia gravis, cerebrovascular accident, cerebral ischaemia.
Eye disorders	Keratitis, decreased corneal sensitivity, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), ptosis, diplopia, choroidal detachment following filtration surgery (see PRECAUTIONS, 6. Special warnings and precautions for use), tearing, corneal erosion.
Ear and labyrinth disorders	Tinnitus.
Cardiac disorders	Bradycardia, chest pain, palpitation, oedema, arrhythmia, congestive heart failure, cardiac arrest, heart block, atrioventricular block, cardiac failure.
Vascular disorders	Hypotension, claudication, Raynaud's phenomenon, cold hands and feet.
Respiratory, thoracic, and mediastinal disorders	Dyspnoea, bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, cough.
Gastrointestinal disorders	Nausea, dyspepsia, diarrhoea, dry mouth, dysgeusia, abdominal pain, vomiting.
Skin and subcutaneous tissue disorders	Alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash.
Musculoskeletal and connective tissue disorders	Systemic lupus erythematosus, myalgia, arthropathy.
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.

2. Pediatric Use
The safety and efficacy of Tapcom-S in children and adolescents below the age of 18 years have not been established. No data are available.
Tapcom-S is not recommended for use in children and adolescents below the age of 18 years.

3. Use in elderly
No dosage alteration in elderly patients is necessary.

4. Use in renal/hepatic impairment
Tafluprost and timolol eye drops have not been studied in patients with renal/hepatic impairment and Tapcom-S should therefore be used with caution in such patients.

5. Precautions concerning Use
1) To reduce the risk of darkening of the eyelid skin the patients should wipe off any excess solution from the skin.
2) When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase of local activity.
3) If more than one topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart.
4) Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.
5) Patients should be instructed to avoid allowing the container to come into contact with the eye or surrounding structures as this could cause injury to the eye.
6) Patients should also be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

6. Special warnings and precautions for use

Systemic effects:
Like other topically applied ophthalmic agents, tafluprost and timolol are absorbed systemically. Due to the beta-adrenergic component timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic adverse reactions after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see PRECAUTIONS, 5. Precautions concerning Use.

Cardiac disorders:
In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.
Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Vascular disorders:
Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders:
Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers. Tapcom-S should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycemia/diabetes:
Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Beta-blockers may also mask the signs of hyperthyroidism. Abrupt withdrawal of beta-blocker therapy may precipitate a worsening of symptoms.

Corneal diseases:
Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Other beta-blocking agents:
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol (a component of Tapcom-S) is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical β-adrenergic blocking agents is not recommended.

Angle-closure glaucoma:
In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol has little or no effect on the pupil. When timolol is used to reduce elevated intraocular pressure in angle-closure glaucoma it should be used with a miotic and not alone.

Anaphylactic reactions:
While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Choroidal detachment:
Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Surgical anaesthesia:
Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation which are related to tafluprost therapy. Some of these changes may be permanent, and may lead to differences in appearance between the eyes when only one eye is treated.

The change in iris pigmentation occurs slowly and may not be noticeable for several months. The change in eye colour has predominantly been seen in patients with mixed coloured irises, e.g. blue-brown, grey-brown, yellow-brown and green-brown. The risk of lifelong heterochromia between the eyes in unilateral cases is obvious.

There is a potential for hair growth to occur in areas where tafluprost solution comes repeatedly in contact with the skin surface.

There is no experience with tafluprost in neovascular, angle-closure, narrow-angle or congenital glaucoma. There is only limited experience with tafluprost in aphakic patients and in pigmentary or pseudoexfoliative glaucoma.

Caution is recommended when using tafluprost in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema or iritis/uveitis.

7. 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

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.
Oral β-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.
Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.
Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

8. Pregnancy and lactation
Pregnancy
There are no or limited amount of data from the use of Tapcom-S in pregnant women.

Women of childbearing potential have to use effective contraception during Tapcom-S treatment.

Tapcom-S should not be used during pregnancy unless clearly necessary (in case no other treatment options are available).

Tafluprost:
There are no adequate data for the use of tafluprost in pregnant women. Tafluprost can have harmful pharmacologic effects on pregnancy and/or the fetus/newborn child. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Timolol:
There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see PRECAUTIONS, 5. Precautions concerning Use.
Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If Tapcom-S is administered until delivery, the neonate should be carefully monitored during the first days of life.

Breast-feeding
Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see PRECAUTIONS, 5. Precautions concerning Use.
It is unknown whether tafluprost and/or its metabolites are excreted in human milk. Available toxicological data in animals have shown excretion of tafluprost and/or its metabolites in milk. However, at therapeutic doses of tafluprost in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms in the infant.
As a precautionary measure lactation is not recommended if treatment with Tapcom-S is required.

Fertility
There are no data on the effects of Tapcom-S on human fertility.

9. Effects on ability to drive and use machine
No studies on the effects of Tapcom-S on the ability to drive and use machines have been performed. If adverse reactions such as transient blurred vision occurs at instillation, the patient should not drive or operate machinery until the patient feels well and has clear vision.

10. Overdose
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 PRECAUTIONS, 1. Adverse Reactions).
If overdose with Tapcom-S occurs, treatment should be symptomatic and supportive. Timolol does not dialyse readily.

PHARMACEUTICAL PARTICULARS
1. List of excipients
Glycerol
Disodium phosphate dodecahydrate
Disodium edetate
Polysorbate 80
Hydrochloric acid and/or sodium hydroxide for pH adjustment
Water for injections.

2. Incompatibilities
Not applicable

3. Shelf life
Please refer to the EXP date on outer carton.
After first opening a foil pouch: 1 month.

4. Special precautions for storage
Store in a refrigerator (2°C - 8°C) under protection from light.
After opening the foil pouch:
Store at below 25°C under protection from light.

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