

PRODUCT INFORMATION

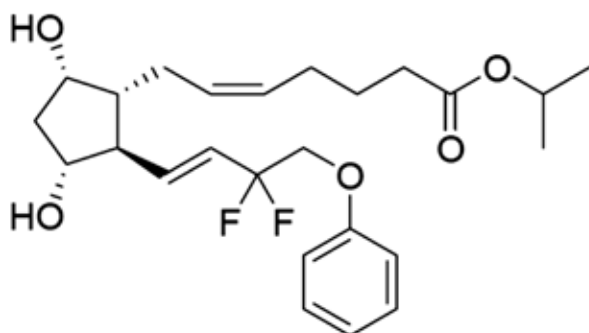
TAPTIQOM 15/5

NAME OF THE MEDICINE

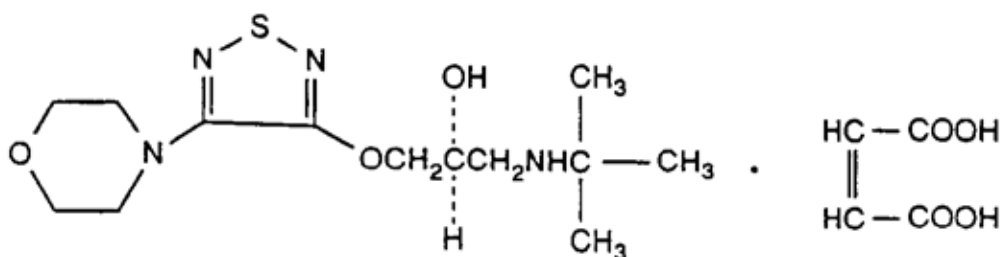
Tafluprost / timolol

Chemical Structure

Tafluprost



Timolol maleate



CAS Numbers

Tafluprost: 209860-87-7

Timolol: 26921-17-5

DESCRIPTION

A clear, colourless solution.

Tafluprost

The chemical name for tafluprost is 1-methylethyl (5Z)-7-[(1R, 2R, 3R, 5S)-2-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxycyclopentyl]-5-heptenoate. The empirical formula of tafluprost is C₂₅H₃₄F₂O₅ and its molecular weight is 452.53.

Tafluprost is a colourless to light yellow viscous liquid that is practically insoluble in water.

Timolol maleate

Timolol maleate is a beta-adrenergic receptor blocking agent. The chemical name is (S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (Z)-2-butenedioate(1:1) (salt). Timolol maleate possesses an asymmetric carbon atom in the structure and is provided as the levo isomer. The empirical formula is $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$.

Timolol maleate has a molecular weight of 432.50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol. Timolol maleate is stable at room temperature.

Qualitative and Quantitative Composition

One millilitre solution contains: tafluprost 15 micrograms and timolol (as maleate) 5 mg.

List of excipients

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

PHARMACOLOGY

TAPTIQOM 15/5 is a fixed combination of two active ingredients: tafluprost, a prostaglandin analogue, and timolol maleate, a beta blocker. These two components of TAPTIQOM 15/5 lower intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone.

Mechanism of Action

Tafluprost

Tafluprost is a fluorinated analogue of prostaglandin $F_{2\alpha}$. Tafluprost acid, the biologically active metabolite of tafluprost, is a highly potent and selective agonist of the human prostanoid FP receptor. Tafluprost acid has sub-nanomolar affinity for the FP receptor (K_i , 0.4 nM), 12-fold higher than that of latanoprost acid.

Reduction of the intraocular pressure in humans starts about 2 to 4 hours after administration and maximum effect is reached 12 hours after instillation. The effect is maintained for at least 24 hours.

Pharmacodynamic studies in monkeys indicate that tafluprost reduces intraocular pressure by increasing the uveoscleral outflow of aqueous humour.

Timolol maleate

Timolol maleate is a nonselective b-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol maleate combines reversibly with a part of the cell membrane, the b-adrenergic receptor, and thus inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the b-adrenergic receptors by catecholamines having b-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of the agonist, which will restore the usual biologic response.

The precise mechanism of action of timolol in lowering intraocular pressure is not clearly established at this time. Pharmacodynamic studies in rabbits and monkeys indicate that timolol mainly reduces intraocular pressure by reducing the formation of aqueous humour.

Pharmacodynamics

Tafluprost

Tafluprost in clinical doses has not been found to have any significant pharmacological effects on the cardiovascular system.

Timolol maleate

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

Pharmacokinetics

Absorption

Plasma concentrations of tafluprost acid and timolol were investigated in healthy volunteers after single and repeated ocular dosing for eight days of TAPTIQOM 15/5 (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 TAPTIQOM 15/5 dosing. Accumulation of tafluprost acid was negligible and the tafluprost acid mean AUC_{0-last} (monotherapy: 4.45 ± 2.57 pg·h/mL; TAPTIQOM 15/5: 3.60 ± 3.70 pg·h/mL) and the mean C_{max} (monotherapy: 23.9 ± 11.8 pg/mL; TAPTIQOM 15/5: 18.7 ± 11.9 pg/mL) were both slightly lower with TAPTIQOM 15/5 as compared to tafluprost monotherapy on Day 8. Timolol plasma concentrations peaked at median T_{max} values of 15 and 37.5 minutes after TAPTIQOM 15/5 dosing on Days 1 and 8, respectively. The Day 8 timolol mean AUC_{0-last} (monotherapy: 5750 ± 2440 pg·h/mL; TAPTIQOM 15/5: 4560 ± 2980 pg·h/mL) and the mean C_{max} (monotherapy: 1100 ± 550 pg/mL; TAPTIQOM 15/5: 840 ± 520 pg/mL) were both somewhat lower with TAPTIQOM 15/5 compared to timolol monotherapy. The lower plasma timolol exposure with TAPTIQOM 15/5 appears to be due to once-daily dosing for TAPTIQOM 15/5 versus twice daily dosing with timolol monotherapy.

Tafluprost and timolol are absorbed through the cornea. In rabbits, corneal penetration of tafluprost from TAPTIQOM 15/5 was similar to that of tafluprost monopreparation after a single instillation while the penetration of timolol was slightly less from the TAPTIQOM 15/5 compared to timolol monopreparation. For tafluprost acid, AUC_{4h} in aqueous humour was 7.5 ng·h/mL following administration of TAPTIQOM 15/5 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 TAPTIQOM 15/5 and timolol monopreparation, respectively. T_{max} for tafluprost acid in aqueous humour was 60 min for both TAPTIQOM 15/5 and tafluprost monopreparation, while for timolol T_{max} was 60 min for TAPTIQOM 15/5 and 30 min for timolol monopreparation.

Distribution

Tafluprost

After topical administration of 1 μ g 3 H-tafluprost on the monkey eye, the maximum radioactivity in the aqueous humour was detected at 2 hours (21-30 ng equivalents/mL) and declined to 0.3-0.4 ng equivalents/mL at 24 hours. 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 humour was reached after 30 minutes following a single topical ocular application of ³H-radiolabelled timolol (0.5% solution) in rabbits.

Metabolism

Tafluprost

Tafluprost, an ester prodrug, is hydrolysed to its biologically active acid metabolite in the eye. The principal metabolic pathway of tafluprost in human, which was tested *in vitro* in hepatocytes, is the hydrolysis to the pharmacologically active metabolite, tafluprost acid, which is further metabolised by glucuronidation or beta-oxidation. Products of beta-oxidation, 1,2-dinor and 1,2,3,4-tetranor tafluprost acids, may be glucuronidated or hydroxylated. Cytochrome P450 (CYP) enzymes are 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. Butyrylcholine esterase but not acetylcholine esterase may also contribute to the hydrolysis.

Timolol

Timolol is metabolised in the liver primarily by CYP2D6 enzyme. Timolol and its metabolites are excreted primarily through the kidneys.

Elimination

Tafluprost

In two clinical studies, mean tafluprost acid metabolite concentrations fell below the limit of quantification in plasma (10 pg/mL) 30 minutes after administration, indicating rapid elimination.

Timolol

Apparent elimination half-life from the human plasma is about 4 hours.

Special Populations

Renal Insufficiency

TAPTIQOM 15/5 has not been studied in patients with renal insufficiency and should therefore be used with caution in such patients.

Hepatic Insufficiency

TAPTIQOM 15/5 has not been studied in patients with hepatic insufficiency and should therefore be used with caution in such patients.

Pulmonary Insufficiency

TAPTIQOM 15/5 has not been systematically studied in patients with pulmonary insufficiency and should therefore be used with caution in such patients.

CLINICAL TRIALS

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 TAPTIQOM 15/5 (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). TAPTIQOM 15/5 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 TAPTIQOM 15/5 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 TAPTIQOM 15/5 or the same monotherapy. The mean diurnal IOP reduction of TAPTIQOM 15/5 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 TAPTIQOM 15/5 at 3 months was 9 mmHg, in comparison to 7 mmHg observed for both monotherapies. IOP decreases with TAPTIQOM 15/5 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 TAPTIQOM 15/5 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.

INDICATIONS

TAPTIQOM 15/5 is indicated for the reduction of intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to beta blockers or prostaglandin analogues and require a combination therapy.

CONTRAINDICATIONS

TAPTIQOM 15/5 is contraindicated in patients with hypersensitivity to the active substances or to any of the excipients.

Reactive airway disease, bronchospasm, bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease.

Sinus bradycardia; sino-atrial block; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock.

PRECAUTIONS

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 drug reactions (ADRs) after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see DOSAGE AND ADMINISTRATION.

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. TAPTIQOM 15/5 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.

Hypoglycaemia/diabetes

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycaemic agents. Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycaemia.

Hyperthyroidism

Beta-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

Other beta-blocking agents

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when TAPTIQOM 15/5 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 beta-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, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine 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

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Other

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. Unilateral treatment can result in permanent heterochromia.

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.

Macular oedema, including cystoid macular oedema, has been reported during treatment with prostaglandin F_{2α} analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular oedema. Therefore, caution is recommended when using tafluprost in these patients. Caution is also recommended in patients with known risk factors for iritis/uveitis.

Patients should be advised that if they develop an intercurrent ocular condition (e.g. trauma, ocular surgery or infection) or any ocular reactions, particularly conjunctivitis and lid reactions they should immediately seek their physician's advice concerning the continued use of the product.

Effects on fertility

No studies on the effect on fertility have been conducted with tafluprost and timolol in combination.

In male and female rats, no adverse effects on mating performance, fertility or early embryonic development were observed with intravenous dosing of tafluprost at up to 100 µg/kg/day, yielding systemic exposure to tafluprost acid over 14000-times the maximum clinical exposure based on C_{max} or greater than 3600-times based on AUC.

Reproduction and fertility studies with timolol in rats showed no adverse effect on male or female fertility at oral doses up to 150 mg/kg/day.

Use in Pregnancy (Category C)

There are no adequate data for the use of TAPTIQOM 15/5 in pregnant women. No studies on the effect on embryofetal development of tafluprost and timolol in combination in animals have been performed.

Women of childbearing potential have to use effective contraception during TAPTIQOM 15/5 treatment.

TAPTIQOM 15/5 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 pharmacological effects on pregnancy and/or the fetus/newborn child. The potential risk for humans is unknown.

In embryofetal development studies, tafluprost administered intravenously caused increases in post-implantation losses in rats and rabbits and reductions in fetal body weights in rats. Tafluprost also increased the incidence of spine malformations and vertebral skeletal variations in rats and the incidence of skull, brain and spine malformations in rabbits. In the rats, there were no adverse effects on embryofetal development at 3 µg/kg/day, yielding maternal plasma levels of tafluprost acid that were 343-times the maximum clinical exposure based on C_{max} . In rabbits, effects were seen at doses ≥ 0.03 µg/kg/day, producing maternal plasma levels of tafluprost acid during the critical period of development that were 5.3-times higher than the clinical exposure based on C_{max} . At the no effect dose in rabbits, maternal plasma levels of tafluprost acid were below the lower limit of quantification (20 pg/mL) and less than the clinical C_{max} .

In a pre- and postnatal development study in rats, increased mortality of newborns were observed with tafluprost at ≥ 1 µg/kg/day by intravenous administration (yielding 114-times the clinical C_{max}) and decreased birth weights and delayed development (pinna unfolding) were observed at 10 µg/kg/day.

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 DOSAGE AND ADMINISTRATION. Developmental studies with timolol in mice, rats and rabbits at oral doses up to 50 mg/kg/day demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of the offspring. Doses of 1000 mg/kg/day were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at oral doses of 100 mg/kg/day, in this case without apparent maternotoxicity. Beta-adrenergic blocking agents may cause bradycardia in the fetus and newborn infant. During the final part of pregnancy and parturition these drugs should therefore only be given after weighing the needs of the mother against the risk to the fetus.

Although animal reproduction studies are not always predictive of human response, TAPTIQOM 15/5 should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Use in lactation

TAPTIQOM 15/5 should not be used during breastfeeding.

Timolol has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

A study in lactating rats demonstrated that radiolabeled tafluprost and/or its metabolites (0.1% of the dose) were excreted in milk. 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.

Paediatric Use

Safety and effectiveness of tafluprost in paediatric patients have not been established. Therefore, treatment with TAPTIQOM 15/5 is not recommended.

Use in the elderly

No dosage adjustment is required for elderly patients.

Genotoxicity

Tafluprost was not mutagenic or clastogenic in a battery of genetic toxicology studies, including an *in vitro* microbial mutagenesis assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung cells, and an *in vivo* mouse micronucleus assay in bone marrow.

In vitro and *in vivo* studies (Ames test, neoplastic cell transformation assay, cytogenetic assay and micronucleus test in mice) showed no genotoxicity of timolol.

Carcinogenicity

No carcinogenicity studies have been conducted with tafluprost and timolol in combination.

Tafluprost

Tafluprost was not carcinogenic when administered subcutaneously daily for 24 months at doses up to 30 µg/kg/day in rats and for 18 months at doses up to 100 µg/kg/day in mice (over 1600- and 1300-times, respectively, the maximum clinical exposure based on plasma AUC).

Timolol

In a two-year oral study of timolol maleate in rats there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day, but not at 100 mg/kg/day (approximately 2000 times the maximum recommended human dose of timolol with use of TAPTIQOM, based on mg/m² body surface area).

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinoma in female mice at 500 mg/kg/day, but not at 50 mg/kg/day (approximately 600 times the maximum recommended dose of timolol provided by TAPTIQOM 15/5 therapy on a mg/m² basis). In a subsequent study in female mice, in which post-mortem examinations were limited to uterus and lungs, a statistically significant increase in the incidence of pulmonary tumours was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinoma in mice was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg/day, but not at doses of 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumours has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

INTERACTIONS WITH OTHER MEDICINES

No interaction studies have been performed.

The potential exists for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta blockers solution is administered concomitantly with oral calcium channel blockers, catecholamine-depleting drugs, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

Oral beta-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, SSRIs) and timolol.

Although timolol used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with timolol and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope or postural hypotension.

Oral calcium antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function.

The potential exists for hypotension, AV conduction disturbances and left ventricular failure to occur in patients receiving a beta-blocking agent when an oral calcium entry blocker is added to the treatment regimen. The nature of any cardiovascular adverse effect tends to depend on the type of calcium blocker used. Dihydropyridine derivatives, such as nifedipine, may lead to hypotension, whereas verapamil or diltiazem have a greater propensity to lead to AV conduction disturbances or left ventricular failure when used with a beta-blocker.

Intravenous calcium entry blockers should be used with caution in patients receiving beta-adrenergic blocking agents.

The concomitant use of beta-adrenergic blocking agents and digitalis with either diltiazem or verapamil may have additive effects in prolonging AV conduction time.

ADVERSE EFFECTS

Clinical Trials Experience

In clinical studies, 484 patients have been treated with TAPTIQOM 15/5. The most frequently reported treatment-related adverse event was conjunctival/ocular hyperemia. It occurred in approximately 7% of the patients participating in the clinical studies, 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 TAPTIQOM 15/5 were limited to those earlier reported for either of the single active substances tafluprost or timolol. No new adverse reactions specific for TAPTIQOM 15/5 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.

The following additional drug related adverse reactions have been reported with TAPTIQOM 15/5 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 common	≥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

Attachment 1: Product information for AusPAR Taptiqom 15/5 Tafluprost/Timolol Merck Sharp & Dohme (Australia) Pty Ltd PM-2013-03652-1-5 Final 28 July 2015. This Product Information was approved at the time this AusPAR was published.

Not known	Frequency cannot be estimated
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TAPTIQOM 15/5

System Organ Class	Frequency	Adverse Effects
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 side effects that have been seen with either of the active components in clinical trials or in postmarketing use and may be potential side effects of TAPTIQOM 15/5 are:

Tafluprost

Reduced visual acuity, iris hyperpigmentation, blepharal pigmentation, eye discharge, cataract, allergic conjunctivitis, deepening of eye lid sulcus, iritis/uveitis exacerbation of asthma, dyspnea.

Timolol Maleate

Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localized and generalized rash, depression, insomnia, nightmares, memory loss, dizziness, syncope, paraesthesia, increase in signs and symptoms of myasthenia gravis, cerebrovascular accident, cerebral ischemia, keratitis, blepharoptosis, 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), tinnitus, bradycardia, chest pain, palpitation, oedema, arrhythmia, congestive heart failure, cardiac arrest, heart block, hypotension, claudication, Raynaud's phenomenon, cold hands and feet, dyspnoea, bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, cough, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, alopecia, psoriasiform rash or exacerbation of psoriasis, systemic lupus erythematosus, myalgia, Peyronie's disease, decreased libido, sexual dysfunction, asthenia/fatigue.

DOSAGE AND ADMINISTRATION

General

TAPTIQOM 15/5 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.

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.

Adults

Recommended therapy is one eye drop in the conjunctival sac of the affected eye(s) once daily.

Paediatric Patients

The safety and efficacy of TAPTIQOM 15/5 in children and adolescents below the age of 18 years have not been established. No data are available.

TAPTIQOM 15/5 is not recommended for use in children and adolescents below the age of 18 years.

Geriatric Patients

No dosage alteration in elderly patients is necessary.

Renal Insufficiency

Tafluprost and timolol eye drops have not been studied in patients with renal impairment and should therefore be used with caution in such patients.

Hepatic Insufficiency

Tafluprost and timolol eye drops have not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

Administration

To reduce the risk of darkening of the eyelid skin the patients should wipe off any excess solution from the skin.

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.

If more than one topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart.

Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.

OVERDOSAGE

A topical overdose with tafluprost is not likely to occur.

There have been reports of inadvertent overdose 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 ADVERSE EFFECTS). Timolol does not dialyze readily.

If overdose with TAPTIQOM 15/5 occurs, treatment should be symptomatic and supportive.

Contact the Poisons Information Centre on 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Low-density polyethylene (LDPE) single-dose containers packed in a foil pouch. Each single-dose container has a fill volume of 0.3 mL and there are 10 containers in each foil pouch.

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The following pack sizes are available: 10 x 0.3 mL and 30 x 0.3 mL single-dose containers, single-dose containers.

Shelf life

Unopened foil pouch: 3 years.

Opened foil pouch: 28 days.

Storage

Store the unopened foil pouches in a refrigerator, 2°C – 8°C. Do not freeze. After opening the foil pouch:

- Keep the single-dose containers in the original foil pouch.
- Do not store above 25°C.
- Discard unused single-dose containers after 28 days from date of first opening of the foil pouch.
- Discard an opened single-dose container with any remaining solution immediately after use.

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp and Dohme (Australia) Pty Limited
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POISON SCHEDULE OF THE MEDICINE

Schedule 4 - Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

5 February 2015