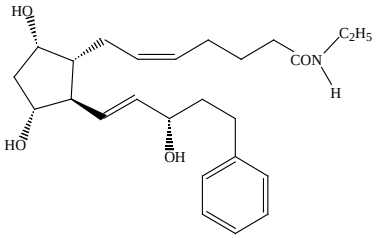
NAME OF THE MEDICINE

GANFORT® PF eye drops

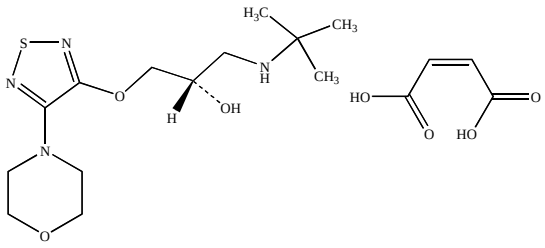
DESCRIPTION

The active constituents of GANFORT® PF eye drops are bimatoprost 0.3 mg/mL and timolol 5.0 mg/mL (with timolol present as timolol maleate).

Chemical structure:



(structure of bimatoprost)



(structure of timolol maleate)

CAS Registry No. 155206-00-1

CAS Registry No. 26921-17-5

Bimatoprost is a synthetic prostamide analogue for ophthalmic use. It is a white to off-white powder and is very soluble in ethyl alcohol, methyl alcohol and slightly soluble in water.
Chemical name: (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-N-ethyl-5-heptenamide
Molecular weight: 415.58
Empirical formula: $C_{25}H_{37}NO_4$
Timolol maleate is a non-selective beta-adrenergic receptor blocking agent. It is a white, odourless, crystalline powder which is soluble in water, methanol and alcohol.
Chemical name: (S)-1-(tert-butylamino)-3- [(4-morpholino-1,2,5-thiadiazol-3-yl) oxy] - 2-propanol maleate (1:1) (salt)
Molecular weight: 432.50 as the maleate salt
Empirical formula: $C_{13}H_{24}N_4O_3S.C_4H_4O_4$

Composition:
GANFORT® PF is a sterile ophthalmic solution in a single dose container.
Each mL of GANFORT® PF contains:
ACTIVES: Bimatoprost 0.3 mg/mL and timolol 5.0 mg/mL
INACTIVES: sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. Contains no antimicrobial agent.

PHARMACOLOGY

Pharmacotherapeutic group: Ophthalmologicals; beta-blocking agents; ATC code: S01ED51

Mechanism of action
GANFORT® PF consists of two active substances: bimatoprost and timolol maleate. These two components decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone. GANFORT® PF has a rapid onset of action.

Bimatoprost
Bimatoprost is a synthetic prostamide analogue with potent ocular hypotensive activity. It selectively mimics the effects of a naturally occurring substance, prostamide. Prostamide is biosynthesised from anandamide by a pathway involving COX-2 but not COX-1, suggesting a new pathway that leads to the synthesis of endogenous lipid amides that lower IOP. Bimatoprost and prostamides differ from prostaglandins (PGs) in that prostamides are biosynthesised from a different precursor, anandamide; bimatoprost does not stimulate any previously described prostanoid receptor; it is not mitogenic; it does not contract the human uterus; and it is electrochemically neutral.

Bimatoprost reduces IOP in man by increasing aqueous humor outflow through the trabecular meshwork and enhancing uveoscleral outflow. Reduction of the IOP starts approximately 4 hours after the first administration and maximum effect is reached within approximately 8 to 12 hours. The duration of effect is maintained for at least 24 hours.

Clinical studies have shown mean IOP decreases of up to 9 mmHg.

Timolol
Timolol maleate is a nonselective beta-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 beta-adrenergic receptor, and thus inhibits the usual biological response that would occur with stimulation of that receptor. The specific competitive antagonism blocks stimulation of the beta-adrenergic receptors by catecholamines having beta-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 biological response.

The precise mechanism of action of timolol maleate in lowering IOP is not clearly established at this time, although a fluorescein study and tonography studies indicate that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

Pharmacokinetics
Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to GANFORT® (multidose) treatment in healthy subjects. Systemic absorption of the individual components was minimal and not affected by co-administration in a single formulation.

In two 12-month studies where systemic absorption was measured, no accumulation was observed with either of the individual components.

Bimatoprost
Bimatoprost penetrates the human cornea and sclera *in vitro*.

After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/mL) within 1.5 hours after dosing. Mean bimatoprost C_{max} values were similar on days 7 and 14 at 0.0721 and 0.0822 ng/mL respectively. The mean $AUC_{0\text{-}24hr}$ values were also similar on days 7 and 14 at 0.0742 and 0.096 ng.hr/mL respectively, indicating that a

steady systemic exposure to bimatoprost was reached during the first week of ocular dosing. The systemic exposure of bimatoprost is very low with no accumulation over time.

Bimatoprost is moderately distributed into body tissues with a steady state systemic volume of distribution in humans of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 90%.

Data from *in vitro* studies showed that the overall extent of melanin binding was not dependent on concentration and the binding was reversible.

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing in humans. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Bimatoprost is eliminated primarily by renal excretion. Up to 67% of an intravenous dose of radiolabelled bimatoprost administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes, the total blood clearance of unchanged bimatoprost was 1.5 L/hr/kg.

After twice daily dosing, the mean $AUC_{0\text{-}24hr}$ value of 0.0634 ng.hr/mL for bimatoprost in the elderly (subjects 65 years or older) was statistically significantly higher than that of 0.0218 ng.hr/mL in young healthy adults, suggesting the existence of an age effect. However, this finding is not clinically relevant as systemic exposure for elderly and young subjects remained very low from ocular dosing. There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients.

Timolol

After ocular administration of a 0.25% eye drop to humans, peak timolol concentration in the aqueous humor was 1.56 µg/mL at 1 hour post dose. The half-life of timolol in plasma is about 7 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma.

CLINICAL TRIALS

Elevated IOP presents a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and glaucomatous visual field loss. Bimatoprost has the action of lowering IOP with no clinically relevant effects on heart rate and blood pressure observed in clinical trials. Timolol decreases aqueous humor production with little or no significant effect on episcleral venous pressure, outflow facility or uveoscleral outflow.

A 12-week (double-masked, randomized, parallel group) clinical study compared the efficacy and safety of GANFORT® PF (single-dose) with GANFORT® (multidose) in patients with glaucoma or ocular hypertension.

A total of 278 and 283 patients were randomised to GANFORT® PF (single dose) and GANFORT® (multidose) treatment groups, respectively. GANFORT® PF single dose achieved noninferior IOP-lowering efficacy to GANFORT® (multidose): the upper limit of the 95% CI of the between-treatment difference was within the pre-defined 1.5 mm Hg margin at each timepoint evaluated (hours 0, 2, and 8) at week 12 (for the primary analysis), and also at weeks 2 and 6, for mean worse eye IOP change from baseline (worse eye IOP refers to the eye with the higher mean diurnal IOP at baseline). The upper limit of the 95% CI did not exceed 0.14 mm Hg at week 12.

The mean change from baseline in worse eye IOP and mean values for worse eye IOP for the PP population are summarised in Table1. The results for the ITT population were similar,

Table 1 Mean Worse Eye IOP (mm Hg) and Mean Change from Baseline in Study 1 (PP Population)

		Worse Eye IOP			Change from Baseline in Worse Eye IOP (Primary Analysis at Week 12)		
Visit	Timepoint	GANFORT PF® (N=256) Mean (SD)	GANFORT® (multidose) (N=260) Mean (SD)	Difference[a] (95% CI)	GANFORT PF® (N=256) Mean (SD)	GANFORT® (multidose) (N=260) Mean (SD)	Difference[a] (95% CI)
Baseline	Hour 0	25.41 (2.232)	25.38 (2.209)	0.01 (-0.35, 0.37)			
	Hour 2	24.79 (2.676)	24.72 (2.470)	0.04 (-0.38, 0.47)			
	Hour 8	23.88 (3.008)	23.82 (2.747)	0.06 (-0.39, 0.50)			
Week 12	Hour 0	16.36 (2.903)	16.68 (2.779)	-0.37 (-0.83, 0.10)	-9.06 (3.216)	-8.72 (3.088)	-0.37 (-0.83, 0.10)
	Hour 2	16.19 (2.969)	16.40 (2.715)	-0.30 (-0.73, 0.14)	-8.53 (3.520)	-8.38 (3.297)	-0.30 (-0.73, 0.14)
	Hour 8	15.87 (2.790)	16.17 (2.612)	-0.36 (-0.78, 0.07)	-7.98 (3.435)	-7.72 (3.172)	-0.36 (-0.78, 0.07)

CI = confidence interval ITT = intent-to-treat PP = per protocol

Worse eye refers to the eye with the worse baseline IOP, which was determined as the eye with the higher mean diurnal IOP at baseline. If both eyes had the same mean diurnal IOP at baseline, the right eye was designated as the worse eye.

Both treatment groups showed statistically and clinically significant mean decreases from baseline in worse eye IOP at all follow up timepoints throughout the study ($p < 0.001$). Mean changes from baseline worse eye IOP ranged from -9.16 to -7.98 mm Hg for GANFORT® PF (single-dose) group, and from -9.03 to -7.72 mm Hg for the GANFORT® (multidose) group across the 12-week study.

Both treatment groups showed statistically and clinically significant mean decreases from baseline in average eye IOP at all follow up timepoints hours 0, 2, and 8 at weeks 2, 6 and 12 ($p < 0.001$).

INDICATIONS

GANFORT® PF eye drops are indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

CONTRAINDICATIONS

• Hypersensitivity to the active substances or to any of the excipients.
• Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
• Sinus bradycardia, sick sinus syndrome, sino-atrial nodal block, second or third degree atrioventricular block not controlled with a pacemaker; overt cardiac failure, cardiogenic shock.

PRECAUTIONS

General:
Like other topically applied ophthalmic agents, GANFORT® PF single dose may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed with GANFORT® (multidose). Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-blockers may occur.

Cardiac disorders: Although rare, cardiac reactions have been reported, including death due to cardiac failure.
Caution should be exercised in treating patients with cardiovascular disease (e.g. coronary heart disease, Prinzmetal's angina, first degree heart block and cardiac failure) and hypotension. Patients with a history of cardiac diseases should be watched for deterioration of these diseases and have their pulse rates checked. Cardiac failure should be adequately controlled before beginning GANFORT® PF therapy.

Respiratory Disorder: Although rare, respiratory reactions have been reported, including death, due to bronchospasm. GANFORT® PF should be administered with caution in patients with mild or moderate chronic obstructive pulmonary disease.

Hyperthyroidism: Beta-blockers may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension.

Other beta-blocking agents: Patients who are already receiving a beta-adrenergic blocking agent orally and who are given timolol should be observed closely for a potential additive effect either on the IOP or on the known systemic effects of beta-blockade. The use of two topical beta-adrenergic blocking agents is not recommended.

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.

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency.

Surgical anesthesia: Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anaesthesia in surgical procedures. In patients undergoing elective surgery, it may be necessary to gradually withdraw the beta-adrenergic receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Nervous system disorders: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalised weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Liver and renal function: GANFORT® PF has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.

Anaphylaxis: 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. Such patients may be unresponsive to the usual dose of epinephrine used to treat anaphylactic reactions.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

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

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

Eye disorders: Intraocular inflammation: GANFORT® PF should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

GANFORT® PF has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.

In bimatoprost 0.03% (multidose) studies in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than 1 dose of bimatoprost daily may decrease the IOP-lowering effect. Patients using bimatoprost ophthalmic solutions with other prostaglandin analogs should be monitored for changes to their intraocular pressure.

Cystoid macular oedema has been reported with GANFORT® (multidose) and it has been uncommonly reported (>0.1% to <1%) following treatment with bimatoprost. Therefore, GANFORT® PF should be used with caution in patients with known risk factors for macular oedema (e.g., intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy) or in aphakic patients and pseudophakic patients with a torn posterior lens capsule).

During treatment with GANFORT® (multidose) and GANFORT® PF, darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening) with no consequent untoward ocular effects observed. Periorbital tissue pigmentation has been reported to be reversible in some patients.

Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation since these have been observed during treatment with bimatoprost and GANFORT® (multidose). Some of these changes may be permanent, and may lead to differences in appearance between the eyes if only one eye is treated. After discontinuation of GANFORT® (multidose), pigmentation of iris may be permanent. After 12 months treatment with GANFORT® (multidose), the incidence of iris pigmentation was 0.2%. After 12 months treatment with bimatoprost eye drops alone, the incidence was 1.5% and did not increase following 3 years treatment.

GANFORT® (multidose) has been reported to cause changes to pigmented tissues. The most frequently reported pigmentary changes have been increased pigmentation of periocular skin and eyelash darkening. Periorbital tissue pigmentation has been reported to be reversible in some patients.

There is the potential for hair growth to occur in areas where GANFORT® PF solution comes repeatedly in contact with the skin surface. Thus, it is important to apply GANFORT® PF solution as instructed and to avoid it running onto the cheek or other skin areas.

Patients wearing soft (hydrophilic) contact lenses should be instructed to remove them prior to administration of GANFORT® PF and wait at least 15 minutes after instilling GANFORT® PF before reinserting soft contact lenses.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to avoid eye injury and contamination of eye drops.

Each vial is intended only for a single treatment in the affected eye(s). Discard any remaining solution in the vial immediately after use.

Preclinical Findings:
Repeated dose toxicity studies on GANFORT® (multidose) or bimatoprost and timolol in combination showed no special additional hazard for humans. The ocular and systemic safety profile of the individual components is well established.

Bimatoprost: Ocular administration of bimatoprost in monkeys at concentrations of 0.03% or 0.1% once or twice daily for 6 months to 1 year caused an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. No associated increase in melanocyte number was observed with the pigmentation. It appears that the mechanism of increased iris pigmentation is due to increased stimulation of melanin production in melanocytes and not to an increase in melanocyte number.

Periocular effects were also observed in an intravenous toxicity study at systemic exposures at least 235-fold higher than that observed in humans after ocular administration. No functional or microscopic changes related to the periocular effects were observed. The mechanism of action for the observed periocular changes is unknown.

Carcinogenicity:
Bimatoprost: Long-term studies in mice and rats revealed no evidence of carcinogenicity following oral (by gavage) administration of bimatoprost at doses up to 2 and 1 mg/kg/day, respectively. These doses resulted in systemic bimatoprost levels 85 – 95 times the maximum anticipated human exposure (based on blood AUC). In the rat carcinogenicity study, a dose-related increase in vacuolated corpora lutea was observed. The clinical relevance of this ovarian effect is unclear.

Timolol: In a two-year study of timolol maleate in rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats dosed orally at 300 mg/kg/day, but not at 100 mg/kg/day (approximately 2000 times the maximum recommended dose in humans on a "mg/m^2" basis). In a long term study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinomas in female mice dosed orally at 500 mg/kg/day, but not at 50 mg/kg/day (approximately 600 times the maximum recommended ophthalmic dose in humans on a "mg/m^2" basis).

In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumours was again observed at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas in female mice was associated with elevations in serum prolactin. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumours has been established in humans. In adult women who received oral treatment with timolol maleate at doses up to 60 mg (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Genotoxicity:
Bimatoprost was not mutagenic or clastogenic in a bacterial mutation assay, in a mouse lymphoma test *in vitro* or in a mouse micronucleus test. Both *in vitro* and *in vivo* studies (Ames test, neoplastic cell transformation assay, cytogenetic assay and micronucleus test in mice) showed no genotoxicity of timolol.

Effects on Fertility:

Bimatoprost did not affect fertility in male or female rats at oral doses up to 0.6 mg/kg/day corresponding to 30 – 50 times the expected human exposure (based on blood AUC calculated from total blood concentration).

Reproductive toxicity studies of timolol in rats showed no adverse effects on male or female fertility at oral doses up to 100 mg/kg/day.

Use in Pregnancy:
There are no adequate data on the use of GANFORT® PF in pregnant women.

Bimatoprost: Bimatoprost and/or its metabolites crossed the placenta in rats. In embryofetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost of 0.3 and 0.6 mg/kg/day, respectively, resulting in exposures 15 and 34 times the expected human exposure (based on blood AUC calculated from total blood concentration). Bimatoprost was not teratogenic at up to 0.6 mg/kg/day in mice or rats. At doses of ≥ 0.3 mg/kg/day PO in rats, approximately 20 times the expected human exposure, the gestation length was reduced, embryofoetal losses and peri- and postnatal pup mortality were increased, and pup body weights were reduced.

Timolol: Timolol was not teratogenic in mice, rats or rabbits at oral doses up to 50 mg/kg/day (over 600 times the maximum recommended clinical dose on a "mg/m2" basis), although delayed fetal ossification was observed at this dose in rats. At higher doses, there were increases in resorptions and fetal variations (14 ribs and hypoplastic sternebrae) in mice (1000 mg/kg/day), increased resorptions in rabbits (≥ 90 mg/kg/day), and a decreased number of caudal vertebral bodies and arches as well as an increase in hypoplastic sternebrae in rats (500 mg/kg/day).

Epidemiological studies suggest that owing to their pharmacological effects beta-blockers may reduce placental perfusion, which may result in intrauterine growth retardation, premature delivery, or fetal death. In addition, undesirable effects (e.g. bradycardia and hypoglycaemia) may occur in the fetus and the neonate. There is also an increased risk of cardiac and pulmonary complications in a neonate that has been exposed to a beta-blocker. Consequently, GANFORT® PF should not be used during pregnancy unless clearly necessary.

Use in Lactation:
Bimatoprost: Bimatoprost was excreted in rat milk following PO administration. Increased pup mortality and depressed pup growth occurred when dams were treated PO with bimatoprost from gestation day 7 to lactation day 20 at ≥ 0.3 mg/kg/day, corresponding to exposures approximately 20 times the expected human exposure (based on blood AUC calculated from total blood concentration).

There are no data on the excretion of bimatoprost into human milk or on the safety of bimatoprost exposure in infants.

Timolol: Timolol is excreted in human milk and there is potential for serious adverse reactions from timolol in breastfed infants. Therefore, nursing women who use GANFORT® PF should stop breast feeding.

Paediatric Use:
Safety and effectiveness in paediatric patients have not been established.

Geriatric Use:
No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

INTERACTIONS WITH OTHER MEDICINES

Specific drug interaction studies have not been conducted with GANFORT® PF eye drops.

Patients who are receiving a systemic (e.g., oral or intravenous) beta-adrenergic blocking agent and GANFORT® PF should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure.

There is a potential for additive effects resulting in hypotension, and/or marked bradycardia when eye drops containing timolol are administered concomitantly with oral calcium channel blockers, guanethidine, or beta-blocking agents, anti-arrhythmics (including amiodarone), digitalis glycosides or parasympathomimetics, and other anti-hypertensives.

Although timolol has little or no effect on the size of the pupil, mydriasis has occasionally been reported when timolol has been used with mydriatic agents such as adrenaline.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, selective serotonin reuptake inhibitors (SSRIs), and timolol).

Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia.

Effects on ability to drive and use machines:
GANFORT® PF has negligible influence on the ability to drive and use machines. As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

ADVERSE EFFECTS

Based on a 3 month study of GANFORT® PF single dose administered once daily, the most commonly reported ADR in the GANFORT® PF group was conjunctival hyperaemia in approximately 21% of patients and led to a discontinuation rate of 1.4% in patients. The conjunctival hyperaemia was mostly trace to mild and thought to be of a non-inflammatory nature.

Table 2 presents the undesirable effects considered related to treatment that were reported in ≥ 1% of patients during treatment with GANFORT® PF. Most were ocular, mild and none was serious.

Table 2 Summary of Adverse Reactions in Study 1 in ≥ 1% of Patients in the GANFORT® PF Treatment Group

System Organ Class Preferred Term	GANFORT® PF (Single Dose) N = 278
Eye disorders	
Conjunctival hyperemia	59 (21.2%)
Eye pruritus	12 (4.3%)
Dry eye	9 (3.2%)
Punctate keratitis	8 (2.9%)
Eye pain	7 (2.5%)
Foreign body sensation in eyes	6 (2.2%)
Eye irritation	6 (2.2%)
Growth of eyelashes	4 (1.4%)
Lacrimation increased	4 (1.4%)
Conjunctival irritation	4 (1.4%)
Photophobia	3 (1.1%)
Erythema of eyelid	3 (1.1%)
Nervous system disorders	
Headache	4 (1.4%)
Skin and subcutaneous tissue disorders	
Skin (periocular) hyperpigmentation	11 (4.0%)

Additional adverse reactions reported with GANFORT® (multi-dose) formulation reported in ≥ 1% of patients that may occur with GANFORT® PF single-dose are listed in Table 3 below. Most were ocular, and of mild severity, and none were serious.

Table 3 GANFORT® (multidose)

System Organ Class	Adverse reaction
Eye disorders	corneal erosion, burning sensation, eye discharge, visual disturbance, eyelid pruritus, iris hyperpigmentation, Lid sulcus deepened, cystoid macular oedema, blepheral pigmentation.

Additional adverse reactions that have been seen with one of the components (bimatoprost or timolol) and may potentially occur also with GANFORT® PF are listed below in Table 4 (timolol) and Table 5) (bimatoprost)

Adverse reactions that have been seen with ophthalmic beta-blockers and may potentially occur also with GANFORT® PF single-dose are listed below in Table 4:

Table 4 Timolol

System Organ Class	Adverse reaction
General disorders and administration site conditions	asthenia/fatigue
Immune system disorders	systemic allergic reactions including angioedema, urticaria, localised and generalised rash, pruritus, anaphylaxis, systemic lupus erythematosus
Metabolism and nutrition disorders	hypoglycaemia **(see warnings and precautions)**
Psychiatric disorders	behavioral changes and psychic disturbances including anxiety, confusion, disorientation, hallucinations, nervousness, somnolence, insomnia, depression, nightmares, memory loss
Nervous system disorders	syncope, cerebrovascular accident, dizziness, increase in signs and symptoms of myasthenia gravis, paresthaesia, cerebral ischaemia
Eye disorders	decreased corneal sensitivity, diplopia, ptosis, choroidal detachment following filtration surgery **(see warnings and precautions)**, keratitis, pseudopemphigoid, ptosis, refractive changes, signs and symptoms of ocular irritation including conjunctivitis and blepharoptosis, blepharitis, eye discharge
Cardiac disorder	atrioventricular block, cardiac arrest, arrhythmia, bradycardia **(see contraindications)**, cardiac failure, chest pain, edema, heart block, palpitation, congestive heart failure, pulmonary oedema, worsening of angina pectoris.
Vascular disorders	hypotension, Raynaud's phenomenon, cold hands and feet, claudication
Respiratory, thoracic and mediastinal disorders	bronchospasm (predominantly in patients with pre-existing bronchospastic disease) dyspnoea, cough, nasal congestion, respiratory failure, upper respiratory infection
Gastrointestinal disorders	dysgeusia, diarrhoea, dyspepsia, dry mouth, abdominal pain, vomiting, anorexia
Skin and subcutaneous tissue disorders	alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash
Musculoskeletal and connective tissue disorders	myalgia
Reproductive system and breast disorders	sexual dysfunction, decreased libido, Peyronie's disease, retroperitoneal fibrosis
Ear and Labyrinth disorders	tinnitus

Table 5 Bimatoprost 0.3 mg/ml (multi-dose and single-dose formulations)

System Organ Class	Adverse reaction
Eye disorders	allergic conjunctivitis, conjunctival oedema, erythema (periorbital), eyelash darkening, hair growth abnormal, vision blurred, blepharospasm, eyelid retraction , retinal haemorrhage, asthenopia, blepharitis, iritis, cataract, liver function test abnormal, peripheral edema, uveitis, eye discharge, periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos and eyelid retraction.
Vascular disorders	hypertension
General disorders and administration site condition	asthenia infection (primarily colds)
Gastrointestinal disorders	nausea

Postmarketing Experience – GANFORT® PF (single dose)

The following adverse reactions have been identified during postmarketing use of GANFORT® PF (single dose) in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiac Disorders
Bradycardia

Eye Disorders
Eye swelling, Ocular Discomfort

Immune System Disorders
Hypersensitivity reactions including signs or symptoms of Allergic dermatitis, Angioedema, Eye allergy

Respiratory, Thoracic and Mediastinal Disorders
Asthma, Dyspnea

Skin Disorders
Alopecia, Skin discoloration (periocular)

Vascular Disorders
Hypertension

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of GANFORT® PF in the affected eye(s) once daily, administered either in the morning or in the evening. It should be administered at the same time each day.

Existing literature data for GANFORT® suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing.

In order to minimise systemic absorption of GANFORT® PF eye drops, apply pressure to the tear duct for at least 2 minutes immediately following administration of the drug **(See Precautions)**.

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

The unit dose container is 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.

OVERDOSAGE

No case of overdose has been reported, and is unlikely to occur after ocular administration. If overdosage occurs, treatment should be symptomatic and supportive; a patent airway should be maintained.

Bimatoprost:
Systemic overdose resulting from accidental ingestion: If GANFORT® PF is accidentally ingested, the following information may be useful: in two-week oral rat and mouse studies, doses of bimatoprost up to 100 mg/kg/day did not produce any toxicity. This dose is at least 22 times higher than the amount of bimatoprost to which a 10 kg child would be exposed were it to accidentally ingest the entire content of a package (30 unit dose ampoules; 0.4 mL per ampoule; 12 mL) of bimatoprost 0.03% ophthalmic solution.

Timolol:
There have been reports of inadvertent overdosage with timolol ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, hypotension, bronchospasm, and cardiac arrest. An in vitro hemodialysis study, using ^{14}C timolol added to human plasma or whole blood showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

PRESENTATION AND STORAGE CONDITIONS

GANFORT® PF (bimatoprost) 0.3 mg/mL and (timolol as maleate) 5.0 mg/mL eye drops sterile solution is supplied in single-dose low density polyethylene (LDPE) containers with a twist-off tab. Each single-dose contains 0.4 mL solution.

The two pack sizes are:

- 5 x 0.4 mL single dose containers (physician samples). Five single-dose containers are connected in a strip and packaged in an aluminium pouch.
- 30 x 0.4mL single dose containers. Each five single-dose containers are connected in a strip and two strips are packaged in an aluminium pouch. Three pouches are then placed in an outer carton.

Not all pack sizes may be marketed.

Storage: Keep the single dose container in the aluminium pouch until use. Store below 30°C. Protect from light and moisture. Do not freeze. Once the pouch is opened, keep the single-dose ampoules in the pouch and place the pouch back in carton to protect against light and moisture, use within 10 days.

Shelf life: 2 years.

Discard the opened single-dose container immediately after use.

Prescription Only.

Manufactured by:
Allergan Pharmaceuticals Ireland
Castlebar Road, Westport, County Mayo, Ireland

CCDSv4
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