AUSTRALIAN PRODUCT INFORMATION
GANFORT® 0.3/5 (BIMATOPROST AND TIMOLOL (AS MALEATE)) EYE DROPS

1 NAME OF THE MEDICINE

Bimatoprost and Timolol (as maleate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bimatoprost 0.3 mg/mL and Timolol (as maleate) 5.0 mg/mL

Excipient with known effect: benzalkonium chloride (used as preservative).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Eye drops, solution.

Clear and colourless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

GANFORT® 0.3/5 eye drops are indicated for the reduction of intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to monotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose is one drop of GANFORT® 0.3/5 in the affected eye(s) once daily, administered in the morning.

In order to minimise systemic absorption of GANFORT® 0.3/5 eye drops, apply pressure to the tear duct immediately following administration of the drug (See *Section 4.4 Special warnings and precautions for use*).

As with all eye drops containing benzalkonium chloride as a preservative, there is potential for incompatibility with other topical ophthalmic medications. If more than one topical ophthalmic medicinal product is to be used, other eye drops should not be used within five to ten minutes of using GANFORT® 0.3/5 eye drops.

Information for patients - Use with Contact Lenses

The preservative in GANFORT® 0.3/5 eye drops, benzalkonium chloride, may be absorbed by and cause discolouration of soft contact lenses. Patients wearing soft (hydrophilic) contact lenses should be instructed to remove them prior to administration and wait at least 15 minutes after instilling GANFORT® 0.3/5 eye drops before reinserting soft contact lenses.

Avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to avoid eye injury and contamination of eye drops. Discard contents 4 weeks after opening the bottle.

4.3 CONTRAINDICATIONS

GANFORT® 0.3/5 eye drops are contraindicated in patients with hypersensitivity to any component of this medication, in patients with bronchospasm, bronchial asthma or patients with a history of bronchial asthma or severe chronic obstructive pulmonary disease, in patients with sinus bradycardia, sick sinus syndrome, sino-atrial nodal block, second or third degree atrioventricular block not controlled with a pacemaker, overt cardiac failure or cardiogenic shock.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

GANFORT® 0.3/5 should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

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 doctor's advice concerning the continued use of the product.

GANFORT® 0.3/5 has not been studied in patients with inflammatory ocular conditions, neovascular glaucoma, inflammatory glaucoma, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.

GANFORT® 0.3/5 should not be used alone in the treatment of acute angle-closure 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 analogues should be monitored for changes to their intraocular pressure.

Cystoid macular oedema has been reported with GANFORT® 0.3/5, however, it has been uncommonly reported (>0.1% to <1%) following treatment with bimatoprost. Therefore, GANFORT® 0.3/5 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® 0.3/5, darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening) with no consequent untoward ocular effects have been observed.

Before treatment is initiated, patients should be informed of the possibility of prostaglandin analogue periorbitopathy (PAP) and increased iris pigmentation since these have been observed during treatment with bimatoprost. Some of these changes may be permanent and may lead to impaired field of vision and differences in appearance between the eyes if only one eye is treated (see Section 4.8 Undesirable Effects).

There is the potential for hair growth to occur in areas where GANFORT® PF 0.3/5 solution comes repeatedly in contact with the skin surface. Thus, it is important to apply GANFORT® 0.3/5 solution as instructed and to avoid it running onto the cheek or other skin areas.

Like other topically applied ophthalmic agents, GANFORT® 0.3/5 may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed.

Identified precautions

Due to the beta-adrenergic component, timolol, adverse reactions typical of systemic beta-adrenoceptor blocking agents may occur and include the following:

- *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 accidental, diagnostic or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

- *Cardiac disorders:* Although rare, cardiac reactions have been reported, including death due to cardiac failure. Caution should be exercised in treating patients with severe or unstable and uncontrolled cardiovascular disease (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension. Cardiac failure should be adequately controlled before beginning GANFORT® 0.3/5 therapy. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked. 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. Due to the negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block. Beta-blockers may cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension.

  Cardiac and respiratory reactions, including death due to bronchospasm in patients with asthma, and rarely, death in association with cardiac failures have been reported following administration of timolol maleate.

- *Respiratory Disorder:* Respiratory reactions have been reported, including death, due to bronchospasm. Patients with chronic obstructive pulmonary diseases of mild or moderate severity, should in general, not receive products containing beta-blockers, including GANFORT® 0.3/5; however, if GANFORT® 0.3/5 is deemed necessary in

such patients, it should be administered with caution in such patients and only if the potential benefit outweighs the potential risk.

- *Liver and renal function:* GANFORT® 0.3/5 has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.

  In patients with a history of mild liver disease or abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline, bimatoprost had no adverse reactions on liver function over 24 months. There are no known adverse reactions of ocular timolol on liver function.

- *Hyperthyroidism*: Beta-blockers may also mask the signs of hyperthyroidism.

- *Other beta-blocking agents:* Patients who are already receiving a beta-adrenergic blocking agent orally and who are given timolol should be closely observed 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.

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

- *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- adrenergic blocking agentsmay mask the signs and symptoms of acute hypoglycemia.

- *Surgical anaesthesia:* 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. The anaesthetist must be informed if the patient is using GANFORT® 0.3/5.

- *Muscle weakness:* 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.

- *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.

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

Use in the elderly

See section 5.2 Pharmacokinetic properties

Paediatric use

Safety and effectiveness in paediatric patients have not been established.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Specific drug interaction studies have not been conducted with GANFORT® 0.3/5 eye drops.

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, digitalis glycosides or parasympathomimetics.

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

Potentiated systemic beta-blockade (e.g. decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P450 enzyme, CYP2D6.

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.

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

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 result in vertigo, syncope or postural hypotension.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 – Pregnancy Category C

There are no adequate data on the use of GANFORT® 0.3/5 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, embryofetal 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/m^2" 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® 0.3/5 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® 0.3/5 should stop breast feeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

GANFORT® 0.3/5 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 (see Section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The majority of ADR's were ocular, mild in severity and none were serious.

Based on 12 month clinical data, the most commonly reported ADR in the GANFORT® 0.3/5 group was conjunctival hyperaemia in approximately 26% of patients and led to a discontinuation rate of 1.5% in patients. The conjunctival hyperaemia was mostly trace to mild and thought to be of a non-inflammatory nature.

In the 12 month studies, discontinuations due to adverse events occurred in 6.9% of patients in the GANFORT® 0.3/5 group compared with 9.8% in the bimatoprost group and 3.4% in the timolol group.

The following adverse drug reactions were reported during clinical trials with GANFORT® 0.3/5 eye drops:

Ocular effects
Very Common (>1/10): conjunctival hyperaemia, growth of eyelashes
Common (>1/100, <1/10): burning sensation, eye pruritus, superficial punctate keratitis, eye dryness, foreign body sensation, stinging sensation in the eye, eyelid erythema, photophobia, eye pain, eye discharge, eyelid pruritus, visual disturbance, corneal erosion

Uncommon (>1/1000, <1/100): eye irritation, blepharitis, epiphora, iritis, eyelid oedema, eyelid pain, conjunctival oedema, asthenopia, trichiasis, visual acuity worsened

Nervous system disorders
Uncommon (>1/1000, <1/100): headache

Respiratory, thoracic and mediastinal disorders
Uncommon (>1/1000, <1/100): rhinitis

Skin and subcutaneous tissue disorders
Common (>1/100, <1/10): blepharal pigmentation
Uncommon (>1/1000, <1/100): hirsutism

Post-marketing Experience

In addition to what has been observed in clinical trials, the following adverse reactions have been identified during postmarketing use of GANFORT® 0.3/5. Because postmarketing reporting is voluntary and from a population of uncertain size, it is not possible to reliably estimate the frequency of these reactions.

Cardiac Disorders
Bradycardia

Eye disorders
Cystoid macular oedema, eye swelling, lid sulcus deepened (enophthalmos), iris hyperpigmentation, vision blurred, ocular discomfort.

General Disorders and Administration Site Conditions
Fatigue

Immune System Disorders
Hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy

Nervous System Disorders
Dizziness, dysgeusia
Psychiatric Disorders
Insomnia, nightmare

Respiratory, Thoracic and Mediastinal Disorders
Asthma, dyspnoea

Skin and subcutaneous tissue disorders
Alopecia, skin hyperpigmentation (periocular), skin discolouration (periocular).

Vascular disorders
Hypertension

Additional Adverse Events

Additionally adverse events that have been seen with either one of the components may potentially occur also with GANFORT® 0.3/5.

Bimatoprost

Ocular effects:
Ocular pruritus, allergic conjunctivitis, eyelash darkening, ocular burning, ocular dryness, ocular irritation, pigmentation of periocular skin, tearing, blepharospasm, retinal haemorrhage and eye discharge; prostaglandin analogue periorbitopathy.

Systemic effects:
Nausea, hypertension, asthenia, headache, infection (primarily colds and upper respiratory tract infections), depression and vertigo.

Description of selected adverse reactions:

Prostaglandin analogue periorbitopathy (PAP)

Prostaglandin analogues including GANFORT® can induce periorbital lipodystrophic changes which can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involution of dermatochalasis and inferior scleral show. Changes are typically mild, can occur as early as one month after initiation of treatment with GANFORT®, and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discoloration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.

Iris hyperpigmentation

Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long-term effects of increased iris pigmentation are not known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts become more brownish. Neither naevi nor freckles of the iris appear to be affected by the treatment. At 12 months, the incidence of iris hyperpigmentation with

bimatoprost 0.1 mg/ml eye drops, solution was 0.5%. At 12 months, the incidence with bimatoprost 0.3 mg/ml eye drops, solution was 1.5% and did not increase following 3 years treatment.

Timolol

Ocular effects:
Decreased corneal sensitivity, diplopia, ptosis, pseudopemphigoid, refractive changes, signs and symptoms of ocular irritation including conjunctivitis, keratitis and choroidal detachment following filtration surgery.

Systemic effects:
Refer to Contraindications and Precautions for additional information on the susceptible patient populations.

Arrhythmia, atrioventricular block, , hypotension, syncope, heart block, cerebrovascular accident, cerebral ischaemia, cardiac arrest, cardiac failure, palpitations, worsening of angina pectoris, pulmonary oedema, claudication, Raynaud's phenomenon, cold hands and feet, bronchospasm (predominantly in patients with pre-existing bronchospastic disease) (Uncommon - See *Section 4.4 Special warnings and precautions for use*), exacerbation of asthma, respiratory failure, upper respiratory infection, nasal congestion, cough, chest pain, alopecia, psoriasiform rash or exacerbation of psoriasis, skin rash, signs and symptoms of allergic reactions including anaphylaxis,angioedema, pruritus, urticaria, localised and generalised rash, anxiety, confusion, depression, disorientation, hallucinations, nervousness, somnolence, memory loss, increase in signs and symptoms of myasthenia gravis, paraesthesia, abdominal pain, anorexia, dry mouth, nausea, vomiting, diarrhoea, dyspepsia, decreased libido, Peyronie's disease, retroperitoneal fibrosis, sexual dysfunction, systemic lupus erythematosus, hypoglycaemia, myalgia, and tinnitus.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No case of overdose has been reported with GANFORT® 0.3/5 and is unlikely to occur after ocular administration.

Bimatoprost:
Systemic overdose resulting from accidental ingestion: If GANFORT® 0.3/5 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 expressed as mg/m^2 is at least 70-times higher than the accidental dose of one bottle of GANFORT® 0.3/5 in a 10 kg child.

Timolol:

Symptoms of systemic timolol overdose are: dizziness, headache, shortness of breath,bradycardia, hypotension, bronchospasm and cardiac arrest. A study of patients showed that timolol did not dialyse readily. If overdosage occurs, treatment should be symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

GANFORT® 0.3/5 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® 0.3/5 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 humour 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 non-selective 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.

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 humour production with little or no significant effect on episcleral venous pressure, outflow facility or uveoscleral outflow.

In four well controlled, double blind, 3-arm, parallel group studies the IOP reducing effect of GANFORT® 0.3/5 was compared with bimatoprost and timolol monotherapy. The mean decreases from the baseline in IOP were statistically significant within each treatment group at all timepoints ($p<0.01$). In the pooled analysis of 2 studies, identical in design, decreases of up to 9.6 mmHg are seen in the GANFORT® 0.3/5 group compared with a maximum 8.8 mmHg in the bimatoprost group.

Responder rates using 18 mmHg as the reference point showed statistically significantly more patients treated with GANFORT® 0.3/5 achieved mean diurnal IOP < 18 mmHg at all visits throughout the 12-month study period when compared with bimatoprost monotherapy and with timolol monotherapy (see Table 1 below).

Table 1: Pooled 12-month Studies: Incidence of patients achieving mean diurnal IOP < 18 mmHg at all visits

Mean Diurnal IOP	GANFORT® 0.3/5 N = 533	Bimatoprost N = 265	Timolol N = 263
< 18 mmHg at all visits	232 (43.5%)	95 (35.8%)[a]	49 (18.6%)[b]

[a] $p = 0.021$; [b] $p < 0.001$

The IOP lowering effect of GANFORT® 0.3/5 was maintained over a 12 month period.

5.2 PHARMACOKINETIC PROPERTIES

GANFORT® 0.3/5

Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to GANFORT® 0.3/5 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

Absorption

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.

Distribution

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.

Metabolism

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.

Excretion

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.

<u>Timolol</u>

After ocular administration of a 0.25% eye drop to humans, peak timolol concentration in the aqueous humour 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.

5.3 PRECLINICAL SAFETY DATA

GANFORT® 0.3/5: Repeated dose toxicity studies on 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.

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride, dibasic sodium phosphate heptahydrate, citric acid monohydrate; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

6.2 INCOMPATIBILITIES

The preservative in GANFORT® 0.3/5 eye drops, benzalkonium chloride, may be absorbed by and cause discolouration of soft contact lenses (see *Section 4.2 Dose and method of administration – Information for patients*).

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

To avoid contamination of the solution, keep container tightly closed. Contents are sterile if seal is intact.

6.5 NATURE AND CONTENTS OF CONTAINER

GANFORT® 0.3/5 (bimatoprost) 0.3 mg/mL and (timolol) 5.0 mg/mL eye drops are supplied in white opaque low density polyethylene (LDPE) bottles with polystyrene screw caps. Each bottle has a fill volume of 3 mL; pack size: 1 x 3 mL bottles in a carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

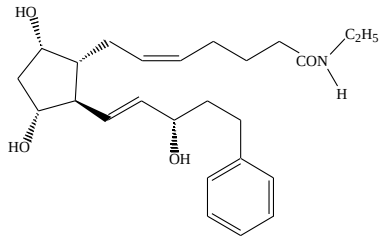
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

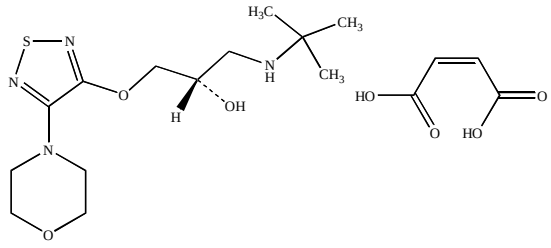
Bimatoprost is a synthetic prostamide analogue for ophthalmic use. It is a white to off-white powder and is very soluble in ethyl alcohol, methyl alcohol and slightly soluble in water.

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 structure



(structure of bimatoprost)



(structure of timolol maleate)

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

Chemical name: (S)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl) oxy] -2-propanol maleate (1:1) (salt)

Molecular weight: 415.58

Molecular weight: 432.50 as the maleate salt

Empirical formula: $C_{25}H_{37}NO_4$

Empirical formula: $C_{13}H_{24}N_4O_3S.C_4H_4O_4$

CAS number

155206-00-1

26921-17-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4, prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

15th May 2009

10 DATE OF REVISION

02 August 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4 Special warnings and	Update to include prostaglandin analogue periorbitopathy (PAP).

precautions for use	
4.8 Undesirable effects	Update under Post marketing experiences prostaglandin analogue periorbitopathy (PAP) and a description for PAP and iris hyperpigmentation under new heading Description of selected adverse reactions

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