# NEW ZEALAND DATA SHEET

# GANFORT® PF - Eye Drops

## 1 PRODUCT NAME

GANFORT® PF 0.3/5 - Eye drops

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1 List of excipients

## 3 PHARMACEUTICAL FORM

Eye Drops

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

GANFORT® PF 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® PF 0.3/5 in the affected eye(s) once daily, administered in the morning.

In order to minimise systemic absorption of GANFORT® PF 0.3/5 eye drops, apply pressure to the tear duct for at least 2 minutes immediately following administration of the drug (see see section 4.4 Special warnings and precautions for use).

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.

**Information for patients - Use with Contact Lenses**

Patients wearing soft (hydrophilic) contact lenses should be instructed to remove them prior to administration of GANFORT® PF 0.3/5 and wait at least 15 minutes after instilling GANFORT® PF 0.3/5 before reinserting soft contact lenses.

**Special Populations**

*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.

## 4.3 Contraindications

GANFORT® PF 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® PF 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® PF 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® PF 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 analogs should be monitored for changes to their intraocular pressure.

Cystoid macular oedema has been reported with GANFORT® (multidose formulation), and, it has been uncommonly reported (>0.1% to <1%) following treatment with bimatoprost. Therefore, GANFORT® PF 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® (multidose) and GANFORT® PF 0.3/5, darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening) with no consequent untoward ocular effects were observed. Periorbital tissue pigmentation has been reported to be reversible in some patients.

Increased iris pigmentation was also reported with GANFORT® (multidose). The change in iris pigmentation occurs slowly and may not be noticeable for several months to years. Neither nevi nor freckles of the iris appear to be affected by treatment. After 12 months of treatment with GANFORT® (multidose), the incidence of iris pigmentation was 0.2%. After 12 months of treatment with bimatoprost eye drops alone, the incidence was 1.5% and did not increase following 3 years of treatment. 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 iridial pigmentation are not known.

Before treatment is initiated, patients should be informed of the possibility of eyelash growth, and periorbital skin hyperpigmentation and increased iris pigmentation since these have been observed during treatment with GANFORT® PF 0.3/5. Some of these changes may be permanent, and may lead to differences in appearance between the eyes if only one eye is treated.

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® PF 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® PF 0.3/5 may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed with GANFORT® (multidose formulation).

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 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 cardiovascular disease (e.g. coronary heart disease, Prinzmetal's angina 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 0.3/5 therapy.

  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:* Although rare, 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® PF 0.3/5; however, if GANFORT® PF 0.3/5 is deemed necessary in such patients, it should be administered with caution in patients and only if the potential benefit outweighs the potential risk.

- *Liver and renal function:* GANFORT® PF 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 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.

- *Choroidal detachment:* Choroidal detachment after filtration procedures 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 hypoglycaemia or to diabetic patients (especially those with labile diabetes) as beta- adrenergic blocking agents may mask the signs and symptoms of acute hypoglycaemia.

- *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® PF 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.

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.

### 4.5 Interaction with other medicines and other forms of interaction

Specific drug interaction studies have not been conducted with GANFORT® PF 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, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, selective serotonin reuptake inhibitors (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.

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

### Pregnancy Category C

There are no adequate data on the use of GANFORT® PF 0.3/5 in pregnant women.

**Bimatoprost:** In embryo/foetal development studies in pregnant mice and rats abortion but no developmental effects were observed at doses that were at least 33 or 97 times higher, respectively, than the intended human exposure. In peri/postnatal studies in rats, reduced gestation time, foetal death and decreased pup body weights were observed in dams given ≥ 0.3 mg/kg/day (a rodent-specific pharmacological effect; systemic exposure estimated to be at least 41 times the intended human exposure). This maternal toxicity likely resulted in decreased mating performance and gestational body weight gain in the offspring, but neurobehavioural functions were not affected.

**Timolol:** Timolol was not teratogenic in mice, rats or rabbits at oral doses up to 50 mg/kg/day (over 300 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 foetal death. In addition, undesirable effects (e.g. bradycardia and hypoglycaemia) may occur in the foetus 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 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 41 times the expected human exposure.

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 0.3/5 should stop breast feeding.

**Fertility**

Bimatoprost did not affect fertility in male or female rats at oral doses up to 0.6 mg/kg/day (approximately 103 times the intended human exposure).

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.

## 4.7 Effects on ability to drive and use machines

GANFORT® PF 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.

## 4.8 Undesirable effects

Based on a 3 month study of GANFORT® PF 0.3/5 single dose administered once daily, the most commonly reported ADR in the GANFORT® PF 0.3/5 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 1 presents the undesirable effects considered related to treatment that were reported in ≥ 1% of patients during treatment with GANFORT® PF 0.3/5. Most were ocular, mild and none was serious.

**Table 1 Summary of Adverse Reactions in Study 1 in ≥ 1% of Patients in the GANFORT® PF 0.3/5 Treatment Group**

| System Organ Class<br>Preferred Term | GANFORT® PF 0.3/5 (Single Dose)<br>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%) |

## Post-marketing Experience

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

*Cardiac Disorders*
Bradycardia

*Eye disorders*
Eye swelling, Ocular discomfort

*Immune system disorders*
Hypersensitivity reactions including sign or symptoms of allergic dermatitis, angioedema, eye allergy

*Respiratory, thoracic and mediastinal disorders*
Asthma, dyspnea

*Skin Disorders*
Alopecia, Skin discoloration (periocular)

*Vascular disorders*
Hypertension

## Additional Adverse Events

Additional adverse reactions reported with GANFORT® (multi-dose) formulation reported in ≥ 1% of patients that may occur with GANFORT® PF 0.3/5 single-dose are listed in Table 2 below. Most were ocular, and of mild severity, and none were serious.

**Table 2 GANFORT® (multidose)**

| System Organ Class | Adverse reaction |
|---|---|
| *Eye disorders* | corneal erosion, burning sensation, eye discharge, visual disturbance, eyelid pruritus, iris hyperpigmentation, deepening of eyelid sulcus, cystoid macular oedema. |

Additional adverse reactions that have been seen with one of the components (bimatoprost) or (timolol) and may potentially occur also with GANFORT® PF 0.3/5 are listed below in Table 3 (timolol) and Table 4 (bimatoprost).

Adverse reactions that have been seen with ophthalmic beta-blockers and may potentially occur also with GANFORT® PF 0.3/5 single-dose is listed below in Table 4:

**Table 3 Timolol**

| System Organ Class | Adverse reaction |
|---|---|
| *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, refractive changes, signs and symptoms of ocular irritation including conjunctivitis and blepharoptosis |
| *Cardiac disorders* | atrioventricular block, cardiac arrest, arrhythmia, **(see contraindications)**, cardiac failure, congestive heart failure, chest pain, palpitations, oedema, heart block, 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), cough, nasal congestion, respiratory failure, upper respiratory infection |
| *Gastrointestinal disorders* | dysgeusia, nausea, 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 |

| System Organ Class | Adverse reaction |
|---|---|
| *General disorders and administration site conditions* | asthenia/fatigue |
| *Ear and Labyrinth disorders* | tinnitus |

**Table 4 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, eyelid oedema, visual acuity worsened, eye discharge |
| *Vascular disorders* | hypertension |
| *General disorders and administration site condition* | asthenia<br>infection (primarily colds) |
| *Gastrointestinal disorders* | nausea |

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/}

## 4.9 Overdose

No information is available on overdose with GANFORT® PF 0.3/5 in humans. If overdose occurs, treatment should be symptomatic and supportive; a patent airway should be maintained.

**Bimatoprost:** Systemic overdose resulting from accidental ingestion: If GANFORT® PF 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 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:** Symptoms of systemic timolol overdose are: dizziness, headache, shortness of breath bradycardia, hypotension, bronchospasm, and cardiac arrest. A study of patients with renal failure showed that timolol did not dialyse readily.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

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

### Mechanism of action

GANFORT® PF 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® PF 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 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 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 efficacy and safety

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 0.3/5 (single-dose) with GANFORT® (multi-dose) in patients with glaucoma or ocular hypertension.

A total of 278 and 283 patients were randomised to GANFORT® PF 0.3/5 (single dose) and GANFORT® (multidose) treatment groups, respectively. GANFORT® PF 0.3/5 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 Table 5.

The results for the ITT population were similar,

**Table 5 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 0.3/5® (N=256) Mean (SD) | GANFORT® 0.3/5 (N=260) Mean (SD) | Difference[a] (95% CI) | GANFORT PF 0.3/5® (N=256) Mean (SD) | GANFORT® 0.3/5 (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, PP = Per=Procotol
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 0.3/5 (single-dose) group, and from -9.03 to -7.72 mm Hg for the GANFORT® 0.3/5 (multi-dose formulation) 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 ($p < 0.001$).

## 5.2 Pharmacokinetic properties

### GANFORT® (multidose)

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

#### 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.

#### Biotransformation

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.

#### Elimination

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.

## 5.3 Preclinical safety data

Repeated dose toxicity studies on bimatoprost and timolol in combination (multidose formulation) showed no special 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 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 and Mutagenicity

**Bimatoprost:** The carcinogenic potential of orally administered (gavage) bimatoprost was evaluated in mice given 0.3, 1.0 or 2.0 mg/kg/day and in rats given 0.1, 0.3 or 1.0 mg/kg/day for 104 weeks. There was no evidence of tumorigenic potential at any of the administered dosages in either species. In the rat carcinogenicity study, a dose-related increase in vacuolated corpora lutea was observed. The ovarian effects in rats are believed to be species specific.

Bimatoprost was not mutagenic or clastogenic in a bacterial mutation assay, in a mouse lymphoma test *in vitro* or in a mouse micronucleus test.

**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 1000 times the maximum recommended ophthalmic 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 300 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.

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.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Each mL of GANFORT® PF 0.3/5 contains:

INACTIVES: sodium chloride, dibasic sodium phosphate heptahydrate, citric acid monohydrate; and water - purified. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH. Contains no antimicrobial agent.

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

2 years

## 6.4 Special precautions for storage

Store below 25°C. Protect from light.

## 6.5 Nature and contents of container

GANFORT® PF 0.3/5 (bimatoprost) 0.3 mg/mL and (timolol) 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 container contains 0.4 mL solution.

The pack sizes are: cartons containing 5 and 30 single-dose; each strip of 5 single-dose containers are packaged in an aluminium foil pouch. Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

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

## 6.7 Physicochemical properties

GANFORT® PF 0.3/5 is a combination eye drop containing bimatoprost and timolol maleate in a preservative free single dose. 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.

# 7 MEDICINE SCHEDULE

Prescription Medicine

# 8 SPONSOR

Allergan New Zealand Limited.
Cr Manu Tapu Dr & Joseph Hammond Place
Auckland International Airport
Mangere, Auckland 1
New Zealand
Toll free telephone: 0800 659 912

# 9 DATE OF FIRST APPROVAL

23 October 2014

# 10 DATE OF REVISION OF THE TEXT

March 2019

**Summary table of changes**

| Section Changed | Summary of new information |
|---|---|
| **4.8** | Addition of AEs in Post-marketing experience section<br>• Ocular discomfort<br>• Alopecia<br>• Skin discoloration (periocular)<br>• Hypertension<br><br>Addition of "Eye discharge" in "Additional AEs" sub-section |
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