ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 0.3 mg of bimatoprost and 5 mg of timolol (as 6.8 mg of timolol maleate).

Excipients
Each ml of solution contains 0.05 mg of benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

4.2 Posology and method of administration

Posology
Recommended dosage in adults (including older people)
The recommended dose is one drop of GANFORT 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 (see section 5.1).

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.

Renal and hepatic impairment
GANFORT has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.

Paediatric population
The safety and efficacy of GANFORT in children aged 0 to 18 years has not been established. No data are available.

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

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block, not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic medicinal products, the active substances (timolol/ bimatoprost) in GANFORT may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-blockers may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders
Patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

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

Respiratory disorders:
Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.

GANFORT should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycaemia/diabetes
Beta-adrenergic blocking medicinal products should be administered with caution in patients subject to spontaneous hypoglycemia or to patients with labile diabetes as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

Beta-blockers may also mask the signs of hyperthyroidism.

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

Other beta-blocking agents
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta- blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5).

Anaphylactic reactions

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

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

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

Hepatic
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.

Ocular
Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid or periocular skin and increased brown iris pigmentation since these have been observed during treatment with bimatoprost and GANFORT. Increased iris pigmentation is likely to be permanent, and may lead to differences in appearance between the eyes if only one eye is treated. After discontinuation of GANFORT, pigmentation of iris may be permanent. After 12 months treatment with GANFORT, 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. 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. Iris color changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Neither nevi nor freckles of the iris appear to be affected by treatment. Periorbital tissue pigmentation has been reported to be reversible in some patients.

Macular oedema, including cystoid macular oedema, has been reported with GANFORT. Therefore, GANFORT should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).
GANFORT should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

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

Excipients
The preservative in GANFORT, benzalkonium chloride, may cause eye irritation. Contact lenses must be removed prior to application, with at least a 15-minute wait before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Contact with soft contact lenses must be avoided.

Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Therefore monitoring is required with frequent or prolonged use of GANFORT in dry eye patients or where the cornea is compromised.

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

In studies of bimatoprost 0.3 mg/ml 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 GANFORT with other prostaglandin analogs should be monitored for changes to their intraocular pressure.

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with the bimatoprost / timolol fixed combination.

There is a potential for additive effects resulting in hypotension, and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly with oral calcium channel blockers, guanethidine, beta-adrenergic blocking agents, parasympathomimetics, anti-arrhythmics (including amiodarone) and digitalis glycosides.

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

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of the bimatoprost / timolol fixed combination in pregnant women. GANFORT should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Bimatoprost
No adequate clinical data in exposed pregnancies are available. Animal studies have shown reproductive toxicity at high maternotoxic doses (see section 5.3).

Timolol
Epidemiological studies have not revealed malformative effects but shown a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If GANFORT is administered until delivery, the neonate should be carefully monitored during the first days of life. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice (see section 5.3).

Lactation
Timolol
Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

Bimatoprost
It is not known if bimatoprost is excreted in human breast milk but it is excreted in the milk of the lactating rat. GANFORT should not be used by breast-feeding women.

Fertility
There are no data on the effects of GANFORT on human fertility.

4.7 Effects on ability to drive and use machines

GANFORT 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 machines.

4.8 Undesirable effects

GANFORT

Summary of the safety profile

The adverse reactions reported in clinical studies using GANFORT were limited to those earlier reported for either of the single active substances bimatoprost and timolol. No new adverse reactions specific for GANFORT have been observed in clinical studies.

The majority of adverse reactions reported in clinical studies using GANFORT were ocular, mild in severity and none were serious. Based on 12-month clinical data, the most commonly reported adverse reaction was conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in approximately 26% of patients and led to discontinuation in 1.5% of patients.

Tabulated list of adverse reactions

The following adverse reactions have been reported with GANFORT (within each frequency grouping, adverse reactions are presented in order of decreasing seriousness).
The frequency of possible adverse reactions listed below is defined using the following convention:

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

System Organ Class	**Frequency**	**Adverse reaction**
Nervous system disorders	Common	Headache, dizziness
Eye disorders	Very common	conjunctival hyperaemia.
	Common	superficial punctuate keratitis, corneal erosion, burning sensation, eye pruritus, stinging sensation in the eye, foreign body sensation, eye dryness, eyelid erythema, eye pain, photophobia, eye discharge, visual disturbance, eyelid pruritus, visual acuity worsened, blepharitis, eyelid oedema, eye irritation, epiphora, growth of eyelashes.
	Uncommon	iritis, conjunctival oedema, eyelid pain, asthenopia, trichiasis, iris hyperpigmentation, deepening of eyelid sulcus, eyelid retraction.
	Not known	cystoid macular oedema.
Respiratory, thoracic and mediastinal disorders	Common	rhinitis

	Uncommon	dyspnoea
	Not known	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)
Skin and subcutaneous tissue disorders	Common	blepharal pigmentation, hirsutism, periocular skin hyperpigmentation.

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

Bimatoprost

System Organ Class	**Adverse reaction**
Eye disorders	allergic conjunctivitis, eyelash darkening, blepharospasm, retinal haemorrhage, uveitis, periorbital erythema, blurred vision.
Vascular disorders	hypertension
General disorders and administration site condition	asthenia
Gastrointestinal disorders	Nausea
Investigations	liver function tests (LFT) abnormal

Timolol

Like other topically applied ophthalmic drugs, GANFORT (bimatoprost/timolol) is absorbed into the systemic circulation. Absorption of timolol may cause similar undesirable effects as seen with systemic beta-blocking agents. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Additional adverse reactions that have been seen with ophthalmic beta-blockers and may potentially occur also with GANFORT are listed below:

System Organ Class	**Adverse reaction**
Immune system disorders	Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis
Metabolism and nutrition disorders	Hypoglycaemia
Psychiatric disorders	Insomnia, depression, nightmares, memory loss
Nervous system disorders	Syncope, cerebrovascular accident, increase in signs and symptoms of myasthenia gravis, paraesthesia, cerebral ischaemia
Eye disorders	Decreased corneal sensitivity, diplopia, ptosis, choroidal detachment following filtration surgery (see section 4.4), keratitis, blurred vision
Cardiac disorder	Atrioventricular block, cardiac arrest, arrhythmia, bradycardia, cardiac failure, congestive heart failure, chest pain, palpitations, oedema
Vascular disorders	Hypotension, Raynaud's phenomenon, cold hands and feet.
Respiratory, thoracic and mediastinal disorders	Cough.
Gastrointestinal disorders	Dysgeusia, nausea, diarrhoea, dyspepsia, dry

	mouth, abdominal pain, vomiting
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
General disorders and administration site conditions	Asthenia/fatigue

Adverse reactions reported in phosphate containing eye drops

Cases of corneal calcification have been reported very rarely in association with the use of phosphate eye containing eye drops in some patients with significantly damaged corneas.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V*.

4.9 Overdose

A topical overdose with GANFORT is not likely to occur or to be associated with toxicity.

Bimatoprost
If GANFORT 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 in a 10 kg child.

Timolol
Symptoms of systemic timolol overdose include: bradycardia, hypotension, bronchospasm, headache, dizziness, shortness of breath, and cardiac arrest. A study of patients with renal failure showed that timolol did not dialyse readily.

If overdose occurs treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmological,– beta-blocking agents – ATC code: S01ED51

Mechanism of action
GANFORT consists of two active substances: bimatoprost and timolol. 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 has a rapid onset of action.

Bimatoprost is a potent ocular hypotensive active substance . It is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) that does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. The mechanism of action by which bimatoprost reduces intraocular pressure in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a $beta_1$ and $beta_2$ non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

Clinical effects
The IOP-lowering effect of GANFORT is non-inferior to that achieved by adjunctive therapy of bimatoprost (once daily) and timolol (twice daily).

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.
Paediatric population
The safety and efficacy of GANFORT in children aged 0 to 18 years has not been established.

5.2 Pharmacokinetic properties

GANFORT medicinal product
Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to GANFORT 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 well *in vitro*. After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over time. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes 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 C_{max} and $AUC_{0-24hrs}$ values were similar on days 7 and 14 at approximately 0.08 ng/ml and 0.09 ng•hr/ml respectively, indicating that a steady drug concentration was reached during the first week of ocular dosing.

Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady-state was 0.67 1/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88%.

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. 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 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 was 1.5 1/hr/kg.

Characteristics in older people
After twice daily dosing, the mean $AUC_{0-24hrs}$ value of 0.0634 ng•hr/ml bimatoprost in the elderly (subjects 65 years or older) were significantly higher than 0.0218 ng•hr/ml in young healthy adults. However, this finding is not clinically relevant as systemic exposure for both 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 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/ml in the aqueous humour at one hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 4 to 6 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 medicinal product
Repeated dose ocular toxicity studies on GANFORT showed no special hazard for humans. The ocular and systemic safety profile of the individual components is well established.

Bimatoprost
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential. Studies in rodents produced species-specific abortion at systemic exposure levels 33- to 97-times that achieved in humans after ocular administration.

Monkeys administered ocular bimatoprost concentrations of ≥0.03% daily for 1 year had 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. The increased iris pigmentation appears to be caused by increased stimulation of melanin production in melanocytes and not by an increase in melanocyte number. No functional or microscopic changes related to the periocular effects have been observed, and the mechanism of action for the periocular changes is unknown.

Timolol
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Sodium chloride
Sodium phosphate dibasic heptahydrate
Citric acid monohydrate
Hydrochloric acid or sodium hydroxide (to adjust pH)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Chemical and physical in-use stability has been demonstrated for 28 days at 25°C.

From a microbiological point of view, the in-use storage times and conditions are the responsibility of the user and would normally not be longer than 28 days at 25°C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White opaque low-density polyethylene bottles with polystyrene screw cap. Each bottle has a fill volume of 3 ml.

The following pack sizes are available: cartons containing 1 or 3 bottles of 3 ml. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation 19 May 2006
Date of latest renewal 23 June 2011

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

Detailed information on this medicinal product is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 0.3 mg of bimatoprost and 5 mg of timolol (as 6.8 mg of timolol maleate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution, in single-dose container.

Colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

4.2 Posology and method of administration

Posology
Recommended dosage in adults (including older people)
The recommended dose is one drop of GANFORT single-dose 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 (multi-dose formulation) 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 (see section 5.1).

The single-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.

Renal and hepatic impairment
GANFORT single-dose has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.

Paediatric population
The safety and efficacy of GANFORT single-dose in children aged less than 18 years has not been established. No data are available.

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

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block, not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic medicinal products, the active substances (timolol/ bimatoprost) in GANFORT single-dose may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed with GANFORT (multi-dose formulation). Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions (ADRs) as seen with systemic beta-blockers may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders
Patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and receiving hypotension therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to the negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

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

Respiratory disorders:
Respiratory reactions, including death due to bronchospasm in patients with asthma, have been reported following administration of some ophthalmic beta-blockers.

GANFORT single-dose should be used with caution in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycaemia/diabetes
Beta-adrenergic blocking medicinal products should be administered with caution in patients subject to spontaneous hypoglycaemia or in patients with labile diabetes as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

Beta-blockers may also mask the signs of hyperthyroidism.

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

Other beta-blocking agents
The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to patients already receiving a systemic beta- blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5).

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

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

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

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

Ocular
Before treatment is initiated, patients should be informed of the possibility of eyelash growth, and periorbital skin hyperpigmentation since these have been observed during treatment with GANFORT single-dose. Increased brown iris pigmentation has also been observed during treatment with GANFORT (multi-dose formulation). Increased iris pigmentation is likely to be permanent, and may lead to differences in appearance between the eyes if only one eye is treated. After discontinuation of GANFORT, pigmentation of iris may be permanent. After 12 months of treatment with GANFORT (multi-dose formulation), 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. Iris color changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Neither nevi nor freckles of the iris appear to be affected by treatment. Periorbital tissue pigmentation has been reported to be reversible in some patients.

Macular oedema, including cystoid macular oedema has been reported with GANFORT (multi-dose formulation). Therefore, GANFORT single-dose should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).
GANFORT should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

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

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

In studies of bimatoprost 0.3 mg/ml 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 GANFORT with other prostaglandin analogs should be monitored for changes to their intraocular pressure.

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There is a potential for additive effects resulting in hypotension, and/or marked bradycardia when ophthalmic beta-blocker solution is administered concomitantly with oral calcium channel blockers, guanethidine, beta-adrenergic blocking agents, parasympathomimetics, anti-arrhythmics (including amiodarone) and digitalis glycosides.

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

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of the bimatoprost / timolol fixed combination in pregnant women. GANFORT single-dose should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Bimatoprost
No adequate clinical data in exposed pregnancies are available. Animal studies have shown reproductive toxicity at high maternotoxic doses (see section 5.3).

Timolol
Epidemiological studies have not revealed malformative effects but have shown a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If GANFORT single-dose is administered until delivery, the neonate should be carefully monitored during the first days of life. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice (see section 5.3).

Lactation
Timolol
Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

Bimatoprost
It is not known if bimatoprost is excreted in human breast milk but it is excreted in the milk of the lactating rat. GANFORT single-dose should not be used by breast-feeding women.

Fertility
There are no data on the effects of GANFORT single-dose on human fertility.

4.7 Effects on ability to drive and use machines

GANFORT single-dose has negligible influence on the ability to drive and use machines. As with any topical ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines.

4.8 Undesirable effects

GANFORT single-dose

Summary of the safety profile

The adverse reactions reported in the clinical study using GANFORT single-dose were limited to those earlier reported for either GANFORT (multi-dose formulation) or for the single active substances bimatoprost or timolol. No new adverse reactions specific for GANFORT single-dose have been observed in clinical studies.

The majority of adverse reactions reported with GANFORT single-dose were ocular, mild in severity and none were serious. Based on a 12-week study of GANFORT single-dose administered once daily, the most commonly reported adverse reaction with GANFORT single-dose was conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in approximately 21% of patients and led to discontinuation in 1.4% of patients.

Tabulated list of adverse reactions

Table 1 presents the adverse reactions that were reported during a 12-week clinical study of GANFORT single-dose (within each frequency grouping, adverse reactions are presented in order of decreasing seriousness).

The frequency of possible adverse reactions listed below is defined using the following convention:

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

Table 1

System Organ Class	**Frequency**	**Adverse reaction**
Eye disorders	Very common	conjunctival hyperaemia
	Common	punctate keratitis, eye irritation, conjunctival irritation, eye pruritus, eye pain, foreign body sensation in eyes, dry eye, lacrimation increased, erythema of eyelid, photophobia, growth of eyelashes
	Uncommon	abnormal sensation in the eye, eyelids pruritus, eyelid oedema, asthenopia, eyelash discolouration (darkening)
Nervous system disorders	Common	headache
General disorders and administration site conditions	Uncommon	fatigue
Skin and subcutaneous tissue disorders	Common	skin hyperpigmentation (periocular)

Table 2 lists additional adverse reactions reported with GANFORT (multi-dose formulation) that may potentially occur with GANFORT single-dose. Most were ocular and of mild severity.

Table 2

System Organ Class	Frequency	Adverse reaction
Nervous system disorders	Common	dizziness
Eye disorders	Common	corneal erosion, eye discharge, visual disturbance
	Uncommon	iritis, conjunctival oedema, blepharitis, eyelid pain, visual acuity worsened, trichiasis, iris hyperpigmentation, deepening of eyelid sulcus, eyelid retraction
	Not known	cystoid macular oedema
Respiratory, thoracic and mediastinal disorders	Uncommon	rhinitis, dyspnoea
	Not known	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)
Skin and subcutaneous tissue disorders	Uncommon	hirsutism

Additional adverse reactions that have been seen with either of the active substances (bimatoprost or timolol), and may potentially occur also with GANFORT single-dose, are listed below in Table 3 (bimatoprost) and Table 4 (timolol):

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

Table 3

System Organ Class	Adverse reaction
Eye disorders	allergic conjunctivitis, blepharospasm, retinal haemorrhage, uveitis, vision blurred
Vascular disorders	hypertension
General disorders and administration site condition	asthenia
Gastrointestinal disorders	nausea
Investigations	liver function tests (LFT) abnormal

Timolol

Like other topically applied ophthalmic drugs, GANFORT (bimatoprost/timolol) is absorbed into the systemic circulation. Absorption of timolol may cause similar undesirable effects as seen with systemic beta-blocking agents. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

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

Table 4

System Organ Class	Adverse reaction
Immune system disorders	systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis
Metabolism and nutrition disorders	hypoglycaemia
Psychiatric disorders	insomnia, depression, nightmares, memory loss
Nervous system disorders	syncope, cerebrovascular accident, increase in signs and symptoms of myasthenia gravis, paresthaesia, cerebral ischaemia
Eye disorders	decreased corneal sensitivity, diplopia, ptosis, choroidal detachment following filtration surgery (see section 4.4), keratitis, blurred vision
Cardiac disorder	atrioventricular block, cardiac arrest, arrhythmia, bradycardia, cardiac failure, congestive heart failure, chest pain, palpitations, oedema
Vascular disorders	hypotension, raynaud's phenomenon, cold hands and feet
Respiratory, thoracic and mediastinal disorders	cough
Gastrointestinal disorders	dysgeusia, nausea, diarrhoea, dyspepsia, dry mouth, abdominal pain, vomiting
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
General disorders and administration site conditions	asthenia

Adverse reactions reported in phosphate containing eye drops

Cases of corneal calcification have been reported very rarely in association with the use of phosphate eye containing eye drops in some patients with significantly damaged corneas.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V*.

4.9 Overdose

A topical overdose with GANFORT single-dose is not likely to occur or to be associated with toxicity.

Bimatoprost

If GANFORT single-dose is accidentally ingested, the following information may be useful: in 2-week oral mice and rats studies, doses of bimatoprost up to 100 mg/kg/day did not produce any toxicity; this corresponds to a human equivalent dose of 8.1 and 16.2 mg/kg, respectively. These doses are at least 7.5 times higher than the amount of bimatoprost in an accidental dose of the entire contents of a carton of GANFORT single-dose (90 single-dose containers x 0.4 mL; 36 mL) in a 10 kg child [(36 mL*0.3 mg/mL bimatoprost)/10 kg; 1.08 mg/kg].

Timolol

Symptoms of systemic timolol overdose include: bradycardia, hypotension, bronchospasm, headache, dizziness, shortness of breath, and cardiac arrest. A study of patients with renal failure showed that timolol did not dialyse readily.

If overdose occurs treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmological, beta-blocking agents – ATC code: S01ED51.

Mechanism of action
GANFORT single-dose consists of two active substances: bimatoprost and timolol. 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 single-dose has a rapid onset of action.

Bimatoprost is a potent ocular hypotensive active substance. It is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) that does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. The mechanism of action by which bimatoprost reduces intraocular pressure in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a $beta_1$ and $beta_2$ non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

Clinical effects
A 12-week (double-masked, randomized, parallel group) clinical study compared the efficacy and safety of GANFORT single-dose with GANFORT (multi-dose formulation) in patients with glaucoma or ocular hypertension. GANFORT single dose achieved noninferior IOP-lowering efficacy to GANFORT (multi-dose formulation): 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). In fact, the upper limit of the 95% CI did not exceed 0.14 mm Hg at week 12.

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 (single-dose) group, and

from -9.03 to -7.72 mm Hg for the GANFORT (multi-dose formulation) group across the 12-week study.

GANFORT single-dose also achieved equivalent IOP-lowering efficacy to GANFORT (multi-dose formulation) in average eye and worse eye IOP at each follow-up timepoint at weeks 2, 6 and 12.

Based on studies of GANFORT (multi-dose formulation), the IOP-lowering effect of GANFORT is non-inferior to that achieved by adjunctive therapy of bimatoprost (once daily) and timolol (twice daily).

Existing literature data for GANFORT (multi-dose formulation) 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.

Paediatric population
The safety and efficacy of GANFORT single-dose in children aged less than 18 years has not been established.

5.2 Pharmacokinetic properties

GANFORT medicinal product
Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to GANFORT (multi-dose formulation) 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 of GANFORT (multi-dose formulation) in which systemic absorption was measured, no accumulation was observed of either of the individual components.

Bimatoprost
Bimatoprost penetrates the human cornea and sclera well *in vitro*. After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over time. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes 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 C_{max} and AUC $_{0\text{-}24hrs}$ values were similar on days 7 and 14 at approximately 0.08 ng/ml and 0.09 ng•hr/ml respectively, indicating that a steady drug concentration was reached during the first week of ocular dosing.

Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady-state was 0.67 1/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88%.

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. 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 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 was 1.5 1/hr/kg.

Characteristics in older people
After twice daily dosing of bimatoprost 0.3 mg/ml, the mean AUC $_{0\text{-}24hrs}$ value of 0.0634 ng•hr/ml bimatoprost in the elderly (subjects 65 years or older) were significantly higher than 0.0218 ng•hr/ml in young healthy adults. However, this finding is not clinically relevant as systemic exposure for both

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 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/ml in the aqueous humour at one hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 4 to 6 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 medicinal product
Repeated dose ocular toxicity studies of GANFORT (multi-dose formulation) showed no special hazard for humans. The ocular and systemic safety profile of the individual components is well established.

Bimatoprost
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential. Studies in rodents produced species-specific abortion at systemic exposure levels 33- to 97-times that achieved in humans after ocular administration.

Monkeys administered ocular bimatoprost concentrations of ≥0.03% daily for 1 year had 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. The increased iris pigmentation appears to be caused by increased stimulation of melanin production in melanocytes and not by an increase in melanocyte number. No functional or microscopic changes related to the periocular effects have been observed, and the mechanism of action for the periocular changes is unknown.

Timolol
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium phosphate dibasic heptahydrate
Citric acid monohydrate
Hydrochloric acid or sodium hydroxide (to adjust pH)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Once the pouch is opened, use within 7 days. Discard the opened single-dose container immediately after first use.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the single-dose containers in the pouch in order to protect against light and moisture.

6.5 Nature and contents of container

Clear, single-dose low density polyethylene (LDPE) containers with a twist-off tab.

Each single-dose container contains 0.4 ml solution.

The following pack sizes are available: cartons containing 5, 30 or 90 single-dose containers; 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

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/003 5 single-dose containers
EU/1/06/340/004 30 single-dose containers
EU/1/06/340/005 90 single-dose containers

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation 19 May 2006
Date of latest renewal 23 June 2011

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

Detailed information on this medicinal product is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit a periodic safety update report for this product in accordance set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR SINGLE BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution
bimatoprost/timolol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of solution contains 0.3 mg bimatoprost and 5 mg timolol (as 6.8 mg of timolol maleate).

3. LIST OF EXCIPIENTS

Benzalkonium chloride, sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution, 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Ocular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Remove contact lenses before use.

8. EXPIRY DATE

EXP
Discard four weeks after first opening.
Opened:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GANFORT

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING THREE BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution
bimatoprost/timolol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of solution contains 0.3 mg bimatoprost and 5 mg timolol (as 6.8 mg of timolol maleate)

3. LIST OF EXCIPIENTS

Benzalkonium chloride, sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution, 3 x 3 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Ocular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Remove contact lenses before use.

8. EXPIRY DATE

EXP
Discard four weeks after first opening.
Opened (1)
Opened (2)
Opened (3)

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
Co. Mayo
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

GANFORT

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

GANFORT 0.3 mg /ml + 5 mg/ml eye drops, solution
bimatoprost/timolol
Ocular use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

POUCH CONTAINING STRIP OF 5 SINGLE-DOSE CONTAINERS

1. NAME OF THE MEDICINAL PRODUCT

GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container
bimatoprost/timolol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of solution contains 0.3 mg bimatoprost and 5 mg timolol (as 6.8 mg of timolol maleate).

3. LIST OF EXCIPIENTS

Sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution
5 x 0.4 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Ocular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once the pouch is opened, use the single-dose containers within 7 days.

9. SPECIAL STORAGE CONDITIONS

Keep single-dose containers in the pouch in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the opened single-dose container immediately after use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road,
Westport,
Co. Mayo,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/003-005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

For single use only

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR POUCH CONTAINING STRIP OF 5 SINGLE-DOSE CONTAINERS

1. NAME OF THE MEDICINAL PRODUCT

GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container
bimatoprost/timolol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of solution contains 0.3 mg bimatoprost and 5 mg timolol (as 6.8 mg of timolol maleate).

3. LIST OF EXCIPIENTS

Sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution
5 x 0.4 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Ocular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep single-dose containers in the pouch in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the opened single-dose container immediately after use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road,
Westport,
Co. Mayo,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

For single use only

16. INFORMATION IN BRAILLE

GANFORT single-dose

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING 30 SINGLE-DOSE CONTAINERS (PROVIDED IN 6 POUCHES, EACH CONTAINING 5 SINGLE-DOSE CONTAINERS)

1. NAME OF THE MEDICINAL PRODUCT

GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container
bimatoprost/timolol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of solution contains 0.3 mg bimatoprost and 5 mg timolol (as 6.8 mg of timolol maleate).

3. LIST OF EXCIPIENTS

Sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution
30 x 0.4 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Ocular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep single-dose containers in the pouch in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the opened single-dose container immediately after use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road,
Westport,
Co. Mayo,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

For single use only

16. INFORMATION IN BRAILLE

GANFORT single-dose

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING 90 SINGLE-DOSE CONTAINERS (PROVIDED IN 18 POUCHES, EACH CONTAINING 5 SINGLE-DOSE CONTAINERS)

1. NAME OF THE MEDICINAL PRODUCT

GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container
bimatoprost/timolol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of solution contains 0.3 mg bimatoprost and 5 mg timolol (as 6.8 mg of timolol maleate).

3. LIST OF EXCIPIENTS

Sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution
90 x 0.4 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Ocular use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep single-dose containers in the pouch in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard the opened single-dose container immediately after use.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Allergan Pharmaceuticals Ireland
Castlebar Road,
Westport,
Co. Mayo,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

For single use only

16. INFORMATION IN BRAILLE

GANFORT single-dose

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SINGLE-DOSE CONTAINER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

GANFORT
bimatoprost/timolol

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0,4 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution
Bimatoprost/timolol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What GANFORT is and what it is used for

GANFORT contains two different active substances (bimatoprost and timolol) that both reduce pressure in the eye. Bimatoprost belongs to a group of medicines called prostamides, a prostaglandin analogue. Timolol belongs to a group of medicines called beta-blockers.

Your eye contains a clear, watery liquid that feeds the inside of the eye. Liquid is constantly being drained out of the eye and new liquid is made to replace this. If the liquid cannot drain out quickly enough, the pressure inside the eye builds up and could eventually damage your sight (an illness called glaucoma). GANFORT works by reducing the production of liquid and also increasing the amount of liquid that is drained. This reduces the pressure inside the eye.

GANFORT eye drops are used to treat high pressure in the eye in adults, including the elderly**.** This high pressure can lead to glaucoma. Your doctor will prescribe you GANFORT when other eye drops containing beta-blockers or prostaglandin analogues have not worked sufficiently on their own.

2. What you need to know before you use GANFORT

Do not use GANFORT eye drops, solution

- if you are allergic to bimatoprost, timolol, beta-blockers or any of the other ingredients of GANFORT (listed in section 6)
- if you have now or have had in past respiratory problems such as asthma, severe chronic obstructive bronchitis (severe lung disease which may cause wheeziness, difficulty in breathing and/ or long-standing cough)
- if you have heart problems such as low heart rate, heart block, or heart failure

Warnings and precautions
Before you use this medicine, tell your doctor if you have now or have had in the past

- coronary heart disease (symptoms can include chest pain or tightness, breathlessness or choking), heart failure, low blood pressure,
- disturbances of heart rate such as slow heart beat

- breathing problems, asthma or chronic obstructive pulmonary disease
- poor blood circulation disease (such as Raynaud's disease or Raynaud's syndrome)
- overactivity of the thyroid gland as timolol may mask signs and symptoms of thyroid disease
- diabetes as timolol may mask signs and symptoms of low blood sugar
- severe allergic reactions
- liver or kidney problems
- eye surface problems
- separation of one of the layers within the eyeball after surgery to reduce the pressure in the eye
- known risk factors for macular oedema (swelling of the retina within the eye leading to worsening vision), for example, cataract surgery

Tell your doctor before surgical anaesthesia that you are using GANFORT as timolol may change effects of some medicines used during anaesthesia.
GANFORT may cause your eyelashes to darken and grow, and cause the skin around the eyelid to darken too. The colour of your iris may also go darker over time. These changes may be permanent. The change may be more noticeable if you are only treating one eye.

Children and adolescents
GANFORT should not be used in children and teenagers under 18.

Other medicines and GANFORT
GANFORT can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma. Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Tell your doctor if you are using or intend to use medicines to lower blood pressure, heart medicine, medicines to treat diabetes, quinidine (used to treat heart conditions and some types of malaria) or medicines to treat depression known as fluoxetine and paroxetine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not use GANFORT if you are pregnant unless your doctor still recommends it.

Do not use GANFORT if you are breast-feeding. Timolol may get into your breast milk.
Ask your doctor for advice before taking any medicine during breast-feeding.

Driving and using machines
GANFORT may cause blurred vision in some patients. Do not drive or use machines until the symptoms have cleared.

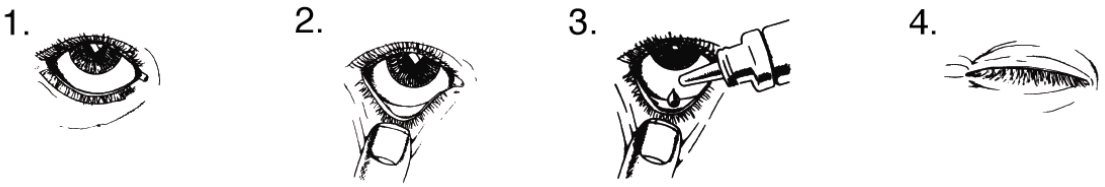
GANFORT contains Benzalkonium chloride
Ganfort contains a preservative called benzalkonium chloride. Benzalkonium chloride may cause eye irritation and is also known to discolour soft contact lenses. Do not use the drops while your contact lenses are in your eyes. Wait at least 15 minutes after using the eye drops before putting your lenses back in your eyes.

3. How to use GANFORT

Always use GANFORT exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual dose is one drop once a day, either in the morning or in the evening in each eye that needs treatment. Use at the same time each day.

Instructions for use
You must not use the bottle if the tamper-proof seal on the bottle neck is broken before you first use it.



5.

1. Wash your hands. Tilt your head back and look at the ceiling.
2. Gently pull down the lower eyelid until there is a small pocket.
3. Turn the bottle upside down and squeeze it to release one drop into each eye that needs treatment.
4. Let go of the lower lid, and close your eye..
5. Whilst keeping the eye closed, press your finger against the corner of the closed eye (the site where the eye meets the nose) and hold for 2 minutes. This helps to stop GANFORT getting into the rest of the body.

If a drop misses your eye, try again.

To avoid contamination, do not let the tip of the bottle touch your eye or anything else. Put the cap back on and close the bottle straight after you have used it.

If you use GANFORT with another eye medicine, leave at least 5 minutes between putting in GANFORT and the other medicine. Use any eye ointment or eye gel last.

If you use more GANFORT than you should
If you use more GANFORT than you should, it is unlikely to cause you any serious harm. Put your next dose in at the usual time. If you are worried, talk to your doctor or pharmacist.

If you forget to use GANFORT
If you forget to use GANFORT, use a single drop as soon as you remember, and then go back to your regular routine. Do not use a double dose to make up for a forgotten dose.

If you stop using GANFORT
GANFORT should be used every day to work properly.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, GANFORT can cause side effects, although not everybody gets them. You can usually carry on taking the drops, unless the effects are serious. If you're worried, talk to a doctor or pharmacist. Do not stop using Ganfort without speaking to your doctor.

The chance of having a side effect is described by the following categories.

Very common	affects more than 1 user in 10
Common	affects 1 to 9 users in 100
Uncommon	affects 1 to 9 users in 1,000
Not known	Frequency cannot be estimated from available data

The following eye side effects may be seen with GANFORT:

Very common: eye redness.

Common: burning, itching, stinging, sensitivity to light, eye pain, sticky eyes, dry eyes, a feeling of something in the eye, small breaks in the surface of the eye with or without inflammation, difficulty in seeing clearly, redness and itching of the eyelids, darkening of the eyelids, darker skin colour around the eyes, headache, longer eyelashes, eye irritation, watery eyes, swollen eyelids, reduced vision, runny nose, hair growing around the eye, dizziness.

Uncommon: iris inflammation, swollen conjunctiva (see-through layer of the eye), painful eyelids, tired eyes, in-growing eyelashes, darker iris colour, eyes appear sunken, eyelid has moved away from the surface of the eye, shortness of breath.

Not known: cystoid macular oedema (swelling of the retina within the eye leading to worsening vision), difficulty breathing / wheezing.

Additional side effects have been seen in patients using eye drops containing bimatoprost and so may possibly be seen with GANFORT:
Allergic reaction in the eye, darkening of the eyelashes, darkening of the iris colour, increased blinking, bleeding in the back of the eye (retinal bleeding), inflammation within the eye
High blood pressure
Weakness
An increase in blood test results that show how your liver is working

Additional side effects have been seen in patients using eye drops containing timolol and so may possibly be seen with GANFORT. Like other medicines applied into eyes, timolol is absorbed into the blood. This may cause similar side effects as seen with ”intravenous” and /or “oral” beta-blocking agents. The chance of having side effects after using eye drops is lower than when medicines are for example, taken by mouth or injected. Listed side effects include reactions seen within the class of beta-blockers when used for treating eye conditions:
Severe allergic reactions with swelling and difficulty breathing which could be life-threatening; allergic reactions (including rash, itching, hives);
Low blood sugar
Difficulty sleeping, nightmares, depression; memory loss
Fainting; stroke; decreased blood flow to the brain; worsening of myasthenia gravis (increased muscle weakness); tingling sensation; dizziness
Decreased sensation of your eye surface; double vision; drooping eyelid; separation of one of the layers within the eyeball after surgery to reduce the pressure in the eye; inflammation of the surface of the eye; blurred vision
Heart failure; irregularity or stopping of the heartbeat; slowing of heart rate; slow or fast heartbeat; too much fluid, mainly water, accumulating in the body; chest pain
Low blood pressure; swelling or coldness of your hands, feet and extremities, caused by constriction of your blood vessels

Cough
Diarrhoea; stomach pain; feeling and being sick; changes in your taste sensation; indigestion; dry mouth
Red scaly patches on skin; skin rash; hair loss
Muscle pain
Reduced sexual urge; sexual dysfunction
Tiredness

Other side effects reported with eye drops containing phosphates
In very rare cases, some patients with severe damage to the clear layer at the front of the eye (the cornea) have developed cloudy patches on the cornea due to calcium build-up during treatment.

If you get any side effects , talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GANFORT

Keep GANFORT out of the sight and reach of children.

Do not use GANFORT after the expiry date which is stated on the bottle label and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Once opened, solutions may become contaminated, which can cause eye infections. Therefore, you must throw away the bottle 4 weeks after you first opened it, even if some solution is left. To help you remember, write down the date that you opened it in the space on the carton.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What GANFORT contains

- The active substances are bimatoprost 0.3 mg/ml and timolol 5 mg/ml corresponding to timolol maleate 6.8 mg/ml.

- The other ingredients are benzalkonium chloride (a preservative), sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate and purified water. Small amounts of hydrochloric acid or sodium hydroxide may be added to bring the solution to the correct pH (acidity) level.

What GANFORT looks like and contents of the pack
GANFORT is a colourless to slightly yellow, clear eye drop solution in a plastic bottle. Each pack contains either 1 or 3 plastic bottles each with a screw-cap. Each bottle is about half full and contains 3 millilitres of solution. This is enough for 4 weeks' usage. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Allergan Pharmaceuticals Ireland
Castlebar Road
Westport

Co. Mayo
Ireland

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien/
Luxembourg/Luxemburg/Nederland
Tél/Tel: +32 (0)2 351 2424

Ireland/Κύπρος/Malta/United Kingdom
Tel: + 44 (0) 1628 494026

България
Тел.: +359 2 962 12 00

Ísland
Sími: + 354 535 7000

Česká republika
Tel: +420 274 008 411

Italia
Tel: + 39 06 509 561

Danmark/Norge/Suomi/Finland/Sverige
Tlf: + 46 (0)8 594 100 00

Magyarország
Tel: +36 1 200 4650

Deutschland/Österreich
Tel: + 49 (0)7243 501 0

Polska
Tel: +48 22 256 37 00

Eesti/Latvija/Lietuva
Tel: +370 5 248 73 50

Portugal
Tel: + 351 21 425 3242

Ελλάδα
Τηλ: +30 210 74 73 300

România
Tel: +40 21 260 13 44

España
Tel: + 34 91 807 6130

Slovenija
Tel: + 386 (0) 590 848 40

France
Tél: + 33 (0)1 49 07 83 00

Slovenská republika
Tel: +421 2 434 150 12

Hrvatska
Tel. + 385 1 6646 563

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

PACKAGE LEAFLET: INFORMATION FOR THE USER

GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container
Bimatoprost/timolol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What GANFORT single-dose is and what it is used for

GANFORT single-dose contains two different active substances (bimatoprost and timolol) that both reduce pressure in the eye. Bimatoprost belongs to a group of medicines called prostamides, a prostaglandin analogue. Timolol belongs to a group of medicines called beta-blockers.

Your eye contains a clear, watery liquid that feeds the inside of the eye. Liquid is constantly being drained out of the eye and new liquid is made to replace this. If the liquid cannot drain out quickly enough, the pressure inside the eye builds up and could eventually damage your sight (an illness called glaucoma). GANFORT single-dose works by reducing the production of liquid and also increasing the amount of liquid that is drained. This reduces the pressure inside the eye.

GANFORT single-dose eye drops are used to treat high pressure in the eye in adults, including the elderly**.** This high pressure can lead to glaucoma. Your doctor will prescribe you GANFORT single-dose when other eye drops containing beta-blockers or prostaglandin analogues have not worked sufficiently on their own.

This medicine does not contain a preservative.

2. What you need to know before you use GANFORT single-dose

Do not use GANFORT single-dose eye drops, solution

- if you are allergic to bimatoprost, timolol, beta-blockers or any of the other ingredients of GANFORT single-dose (listed in section 6)
- if you have now or have had in past respiratory problems such as asthma, severe chronic obstructive bronchitis (severe lung disease which may cause wheeziness, difficulty in breathing and/ or long-standing cough)
- if you have heart problems such as low heart rate, heart block, or heart failure

Warnings and precautions
Before you use this medicine, tell your doctor if you have now or have had in the past

- coronary heart disease (symptoms can include chest pain or tightness, breathlessness or choking), heart failure, low blood pressure
- disturbances of heart rate such as slow heart beat
- breathing problems, asthma or chronic obstructive pulmonary disease
- poor blood circulation disease (such as Raynaud's disease or Raynaud's syndrome)
- overactivity of the thyroid gland as timolol may mask signs and symptoms of thyroid disease
- diabetes as timolol may mask signs and symptoms of low blood sugar
- severe allergic reaction
- liver or kidney problems
- eye surface problems
- separation of one of the layers within the eyeball after surgery to reduce the pressure in the eye
- known risk factors for macular oedema (swelling of the retina within the eye leading to worsening vision), for example, cataract surgery

Tell your doctor before surgical anaesthesia that you are using GANFORT single-dose as timolol may change effects of some medicines used during anaesthesia.

GANFORT single-dose may cause your eyelashes to darken and grow, and cause the skin around the eye to darken too. The colour of your iris may also go darker over time. These changes may be permanent. The change may be more noticeable if you are only treating one eye.

Children and adolescents
GANFORT single-dose should not be used in children and teenagers under 18.

Other medicines and GANFORT single-dose
GANFORT single-dose can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma. Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Tell your doctor if you are using or intend to use medicines to lower blood pressure, heart medicine, medicines to treat diabetes, quinidine (used to treat heart conditions and some types of malaria) or medicines to treat depression known as fluoxetine and paroxetine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not use GANFORT single-dose if you are pregnant unless your doctor still recommends it.

Do not use GANFORT single-dose if you are breast-feeding. Timolol may get into your breast milk. Ask your doctor for advice before taking any medicine during breast-feeding.

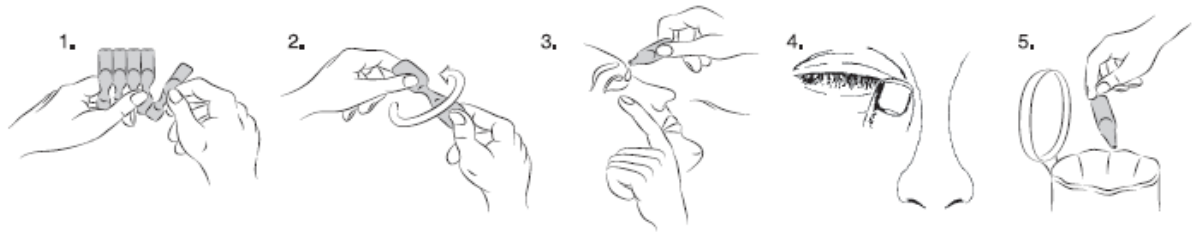
Driving and using machines
GANFORT single-dose may cause blurred vision in some patients. Do not drive or use machines until the symptoms have cleared.

3. How to use GANFORT single-dose

Always use GANFORT single-dose exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual dose is one drop once a day, either in the morning or in the evening in each eye that needs treatment. Use at the same time each day.

Instructions for use
Wash your hands before use. Make sure that the single-dose container is intact before use. The solution should be used immediately after opening. To avoid contamination, do not let the open-end of the single-dose container touch your eye or anything else.



1. Tear 1 single-dose container from the strip.
2. Hold the single-dose container upright (with the cap pointing upwards) and twist off the cap.
3. Gently pull down the lower eyelid to form a pocket. Turn the single-dose container upside down and squeeze it to release 1 drop into the affected eye(s).
4. Whilst keeping the eye closed, press your finger against the corner of the closed eye (the site where the eye meets the nose) and hold for 2 minutes. This helps to stop GANFORT single-dose getting into the rest of the body.
5. Throw away the single-dose container after you have used it, even if there is some solution left.

If a drop misses your eye, try again. Wipe off any excess that runs down the cheek.

If you wear contact lenses, take your lenses out before using this medicine. Wait 15 minutes after using the drops, and before you put your lenses back in.

If you use GANFORT single-dose with another eye medicine, leave at least 5 minutes between putting in GANFORT single-dose and the other medicine. Use any eye ointment or eye gel last.

If you use more GANFORT single-dose than you should
If you use more GANFORT single-dose than you should, it is unlikely to cause you any serious harm. Put your next dose in at the usual time. If you are worried, talk to your doctor or pharmacist.

If you forget to use GANFORT single-dose
If you forget to use GANFORT single-dose, use a single drop as soon as you remember, and then go back to your regular routine. Do not use a double dose to make up for a forgotten dose.

If you stop using GANFORT single-dose
GANFORT single-dose should be used every day to work properly.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, GANFORT single-dose can cause side effects, although not everybody gets them. You can usually carry on taking the drops, unless the effects are serious. If you're worried, talk to a doctor or pharmacist. Do not stop using GANFORT single-dose without speaking to your doctor.

The chance of having a side effect is described by the following categories.

Very common	affects more than 1 user in 10
Common	affects 1 to 9 users in 100
Uncommon	affects 1 to 9 users in 1,000

Not known	Frequency cannot be estimated from available data

The following eye side effects may be seen with GANFORT single-dose:

Very common: eye redness

Common: <u>Affecting the eye</u>
small breaks in the surface of the eye with inflammation, eye irritation, irritation of the conjunctiva (see-through layer of the eye), itchy eyes, eye pain, a feeling of something in the eye, dry eyes, watery eyes, redness of the eyelids, sensitivity to light, longer eyelashes.

<u>Affecting other parts of the body</u>
headache, darker skin colour around the eye.

Uncommon: <u>Affecting the eye</u>
abnormal sensation in the eye, itching of the eyelids, swelling of eyelids, tired eyes, darkening of eyelashes.

<u>Affecting other parts of the body</u>
tiredness.

Additional side effects have been seen in patients using GANFORT (multi-dose formulation) and so may possibly be seen with GANFORT single-dose:
Dizziness, small breaks in the surface of the eye, sticky eye, visual disturbance, iris inflammation, swollen conjunctiva (see through layer of the eye), eyelid inflammation, eyelid pain, reduced vision, ingrowing eyelashes, darkening of the iris colour, sunken eye, eyelid has moved away from the surface of the eye, cystoid macular oedema (swelling of the retina within the eye leading to worsening vision), runny nose, shortness of breath, difficulty in breathing / wheezing, hair growth around the eye.

Additional side effects have been seen in patients using eye drops containing bimatoprost and so may possibly be seen with GANFORT single-dose:
Allergic reaction in the eye, eyelid twitching, bleeding in the back of the eye (retinal bleeding), inflammation within the eye, blurred vision
High blood pressure
Weakness
Nausea
An increase in blood test results that show how your liver is working.

Additional side effects have been seen in patients using eye drops containing timolol and so may possibly be seen with GANFORT single-dose. Like other medicines applied into eyes, timolol is absorbed into the blood. This may cause similar side effects as seen with ”intravenous” and /or “oral” beta-blocking agents. The chance of having side effects after using eye drops is lower than when medicines are for example, taken by mouth or injected. Listed side effects include reactions seen within the class of beta-blockers when used for treating eye conditions:
Severe allergic reactions with swelling and difficulty breathing, which could be life-threatening; allergic reactions (including rash, itching, hives);
Low blood sugar
Difficulty sleeping, nightmares, depression; memory loss
Fainting; stroke; decreased blood flow to the brain; worsening of myasthenia gravis (increased muscle weakness); tingling sensation; dizziness

Decreased sensation of your eye surface; double vision; drooping eyelid; separation of one of the layers within the eyeball after surgery to reduce the pressure in the eye; inflammation of the surface of the eye; blurred vision
Heart failure; irregularity or stopping of the heartbeat; slowing of heart rate; slow or fast heartbeat; too much fluid, mainly water, accumulating in the body; chest pain
Low blood pressure; swelling or coldness of your hands, feet and extremities, caused by constriction of your blood vessels
Cough
Diarrhoea; stomach pain; feeling and being sick; changes in your taste sensation; indigestion; dry mouth
Red scaly patches on skin; skin rash; hair loss
Muscle pain
Reduced sexual urge; sexual dysfunction
Weakness.

Other side effects reported with eye drops containing phosphates
In very rare cases, some patients with severe damage to the clear layer at the front of the eye (the cornea) have developed cloudy patches on the cornea due to calcium build-up during treatment.

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GANFORT single-dose

Keep GANFORT single-dose out of the sight and reach of children.

Do not use GANFORT single-dose after the expiry date which is stated on the single-dose container and the carton. The expiry date refers to the last day of that month.

This medicine is for single use only and does not contain preservatives. Do not keep any unused solution.

This medicinal product does not require any special temperature storage conditions. Keep the single-dose containers in the pouch in order to protect from light and moisture. Once the pouch is opened use within 7 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What GANFORT single-dose contains

- The active substances are bimatoprost 0.3 mg/ml and timolol 5 mg/ml corresponding to timolol maleate 6.8 mg/ml.

- The other ingredients are sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate and purified water. Small amounts of hydrochloric acid or sodium hydroxide may be added to bring the solution to the correct pH (acidity) level.

What GANFORT single-dose looks like and contents of the pack

GANFORT single-dose is a colourless to slightly yellow solution supplied in single-dose plastic containers, each containing 0.4 ml of solution.

Packs contain either 1, 6 or 18 foil pouches, each containing 5-single-dose containers, for a total of 5, 30 or 90 single-dose containers, respectively. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Allergan Pharmaceuticals Ireland
Castlebar Road,
Westport,
Co. Mayo,
Ireland

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien/
Luxembourg/Luxemburg/Nederland
Tél/Tel: +32 (0)2 351 2424

България
Тел.: +359 2 962 12 00

Česká republika
Tel: +420 274 008 411

Danmark/Norge/Suomi/Finland/Sverige
Tlf: + 46 (0)8 594 100 00

Deutschland/Österreich
Tel: + 49 (0)7243 501 0

Eesti/Latvija/Lietuva
Tel: +370 5 248 73 50

Ελλάδα
Τηλ: +30 210 74 73 300

España
Tel: + 34 91 807 6130

France
Tél: + 33 (0)1 49 07 83 00

Hrvatska
Tel. + 385 1 6646 563

Ireland/Κύπρος/Malta/United Kingdom
Tel: + 44 (0) 1628 494026

Ísland
Sími: + 354 535 7000

Italia
Tel: + 39 06 509 561

Magyarország
Tel: +36 1 200 4650

Polska
Tel: +48 22 256 37 00

Portugal
Tel: + 351 21 425 3242

România
Tel: +40 21 260 13 44

Slovenija
Tel: + 386 (0) 590 848 40

Slovenská republika
Tel: +421 2 434 150 12

This leaflet was last revised in <{MM/YYYY}> <{month YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Annex IV

Scientific conclusions and grounds recommending the variation to the terms of the Marketing Authorisation

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for GANFORT, the scientific conclusions of PRAC are as follows:

The PRAC considered that the overall risk/benefit of GANFORT remained favourable.

However, the MAH was recommended that within section 4.8 of the SmPC, the following ADRs be moved from the tables for ADRs seen only with the individual components (timolol and bimatoprost) to the table for ADRs seen with GANFORT: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnea, eyelid retraction and dizziness.

In section 4.8 of the SmPC, the following wording should be added: “Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.”

The above-mentioned SmPC changes will need to be reflected in the PL.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for Ganfort the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing the two active substances bimatoprost and timolol is favourable subject to the proposed changes to the product information, as follows:

Update of section 4.8 of the SmPC

- The Safety information needs amending to reflect the available data. The following ADRs should be moved from the tables for ADRs seen only with the individual components (timolol and bimatoprost) to the ADR table for ADRs seen with GANFORT: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), dyspnea, eyelid retraction and dizziness.

- GANFORT contains a phosphate buffer as an excipient. In line with an assessment of the use of phosphate buffers in medicinal products given as eye drops, the following wording should be added: “Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.”

The CHMP recommends that the terms of the Marketing Authorisation should be varied.