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).

Excipient with known effect
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 (eye drops)

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 elderly)

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

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and 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.

Endocrine disorders

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 colour 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 analogues 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).

Breast-feeding

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

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

Table 1 presents the adverse reactions that have been reported during clinical studies with all GANFORT formulations (multi-dose and single-dose) or in the post-marketing period.

Possible adverse reactions are listed by MedDRA system organ class and are based on 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions with all GANFORT formulations (multi-dose and single-dose)

System Organ Class	Frequency	Adverse reaction
Immune system disorders	Not known	Hypersensitivity reactions

		including signs or symptoms of allergic dermatitis, angioedema, eye allergy
Psychiatric disorders	Not known	Insomnia[2], nightmare[2]
Nervous system disorders	Common	Headache
	Not known	Dysgeusia[2], dizziness
Eye disorders	Very common	Conjunctival hyperaemia.
	Common	Punctuate keratitis, corneal erosion[2], burning sensation[2], conjunctival irritation[1], eye pruritus, stinging sensation in the eye[2], foreign body sensation, dry eye, erythema of eyelid, eye pain, photophobia, eye discharge, visual disturbance[2], eyelid pruritus, visual acuity worsened[2], blepharitis[2], eyelid oedema, eye irritation, lacrimation increased, growth of eyelashes.
	Uncommon	Iritis[2], conjunctival oedema[2], eyelid pain[2], abnormal sensation in the eye[1], asthenopia, trichiasis[2], iris hyperpigmentation[2], periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos, lagophthalmos and eyelid retraction[1&2], eyelash discolouration (darkening)[1].
	Not known	Cystoid macular oedema[2], eye swelling, vision blurred[2], ocular discomfort
Cardiac disorders	Not known	Bradycardia
Vascular disorders	Not known	Hypertension
Respiratory, thoracic and mediastinal disorders	Common	Rhinitis[2]
	Uncommon	Dyspnoea
	Not known	Bronchospasm (predominantly in patients with pre-existing bronchospastic disease)[2], asthma
Skin and subcutaneous tissue disorders	Common	Blepharal pigmentation[2], hirsutism[2], skin hyperpigmentation (periocular).
	Not known	Alopecia, skin discolouration (periocular)
General disorders and administration site conditions	Not known	Fatigue

[1]adverse reactions only observed with Ganfort single-dose formulation
[2]adverse reactions only observed with Ganfort multi-dose formulation

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 either of the active substances (bimatoprost or timolol), and may potentially occur also with GANFORT are listed below in Table 2:

Table 2: List of additional adverse reactions seen with either of the active substances (bimatoprost or timolol)

System Organ Class	Adverse reaction
Immune system disorders	Systemic allergic reactions including anaphylaxis[1]
Metabolism and nutrition disorders	Hypoglycaemia[1]
Psychiatric disorders	Depression[1], memory loss[1], hallucination[1]
Nervous system disorders	Syncope[1], cerebrovascular accident[1], increase in signs and symptoms of myasthenia gravis[1], paraesthesia[1], cerebral ischaemia[1]
Eye disorders	Decreased corneal sensitivity[1], diplopia[1], ptosis[1], choroidal detachment following filtration surgery (see section 4.4)[1], keratitis[1], blepharospasm[2], retinal haemorrhage[2], uveitis[2],
Cardiac disorder	Atrioventricular block[1], cardiac arrest[1], arrhythmia[1], cardiac failure[1], congestive heart failure[1], chest pain[1], palpitations[1], oedema[1]
Vascular disorders	Hypotension[1], Raynaud's phenomenon[1], cold hands and feet[1]
Respiratory, thoracic and mediastinal disorders	Asthma exacerbation[2], COPD exacerbation[2], cough[1]
Gastrointestinal disorders	Nausea[1,2], diarrhoea[1], dyspepsia[1], dry mouth[1], abdominal pain[1], vomiting[1]
Skin and subcutaneous tissue disorders	Psoriasiform rash[1] or exacerbation of psoriasis[1], skin rash[1]
Musculoskeletal and connective tissue disorders	Myalgia[1]
Reproductive system and breast disorders	Sexual dysfunction[1], decreased libido[1]
General disorders and administration site conditions	Asthenia[1,2]
Investigations	Liver function tests (LFT) abnormal[2]

[1] adverse reactions observed with timolol
[2] adverse reactions observed with bimatoprost

Adverse reactions reported in phosphate containing eye drops

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.

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: Ophthalmologicals – antiglaucoma preparations and miotics - beta-blocking agents – timolol, combinations – 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 $_{0\text{-}24hrs}$ 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 l/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 l/hr/kg.

Characteristics in elderly patients

After twice daily dosing, 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 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

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/001
EU/1/06/340/002

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

Detailed information on this medicinal product is available on the website of the European Medicines Agency: https://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 elderly)

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 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 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

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and 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.

Endocrine disorders

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 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 colour 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 analogues 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-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).

Breast-feeding

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 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

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 have been reported during clinical studies with all GANFORT formulations (multi-dose and single-dose) or in the post-marketing period.

Possible adverse reactions are listed by MedDRA system organ class and are based on 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions with all GANFORT formulations (multi-dose and single-dose)

System Organ Class	Frequency	Adverse reaction
Immune system disorders	Not known	Hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy

Psychiatric disorders	Not known	Insomnia[2], nightmare[2]
Nervous system disorders	Common	Headache
	Not known	Dysgeusia[2], dizziness
Eye disorders	Very common	Conjunctival hyperaemia
	Common	Punctuate keratitis, corneal erosion[2], burning sensation[2], conjunctival irritation[1], eye pruritus, stinging sensation in the eye[2], foreign body sensation, dry eye, erythema of eyelid, eye pain, photophobia, eye discharge, visual disturbance[2], eyelid pruritus, visual acuity worsened[2], blepharitis[2], eyelid oedema, eye irritation, lacrimation increased, growth of eyelashes.
	Uncommon	Iritis[2], conjunctival oedema[2], eyelid pain[2], abnormal sensation in the eye[1], asthenopia, trichiasis[2], iris hyperpigmentation[2], periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos, lagophthalmos and eyelid retraction[1&2], eyelash discolouration (darkening)[1].
	Not known	Cystoid macular oedema[2], eye swelling, vision blurred[2], ocular discomfort
Cardiac disorders	Not known	Bradycardia
Vascular disorders	Not known	Hypertension
Respiratory, thoracic and mediastinal disorders	Common	Rhinitis[2]
	Uncommon	Dyspnoea
	Not known	Bronchospasm (predominantly in patients with pre-existing bronchospastic disease)[2], asthma
Skin and subcutaneous tissue disorders	Common	Blepharal pigmentation[2], hirsutism[2], skin hyperpigmentation (periocular).
	Not known	Alopecia, skin discolouration (periocular)
General disorders and administration site conditions	Not known	Fatigue

[1]adverse reactions only observed with Ganfort single-dose formulation
[2]adverse reactions only observed with Ganfort multi-dose formulation

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 either of the active substances (bimatoprost or timolol), and may potentially occur also with GANFORT are listed below in Table 2:

Table 2: List of additional adverse reactions seen with either of the active substances (bimatoprost or timolol)

System Organ Class	Adverse reaction
Immune system disorders	Systemic allergic reactions including anaphylaxis[1]
Metabolism and nutrition disorders	Hypoglycaemia[1]
Psychiatric disorders	Depression[1], memory loss[1], hallucination[1]
Nervous system disorders	Syncope[1], cerebrovascular accident[1], increase in signs and symptoms of myasthenia gravis[1], paraesthesia[1], cerebral ischaemia[1]
Eye disorders	Decreased corneal sensitivity[1], diplopia[1], ptosis[1], choroidal detachment following filtration surgery (see section 4.4)[1], keratitis[1], blepharospasm[2], retinal haemorrhage[2], uveitis[2],
Cardiac disorder	Atrioventricular block[1], cardiac arrest[1], arrhythmia[1], cardiac failure[1], congestive heart failure[1], chest pain[1], palpitations[1], oedema[1]
Vascular disorders	Hypotension[1], Raynaud's phenomenon[1], cold hands and feet[1]
Respiratory, thoracic and mediastinal disorders	Asthma exacerbation[2], COPD exacerbation[2], cough[1]
Gastrointestinal disorders	Nausea[1,2], diarrhoea[1], dyspepsia[1], dry mouth[1], abdominal pain[1], vomiting[1]
Skin and subcutaneous tissue disorders	Psoriasiform rash[1] or exacerbation of psoriasis[1], skin rash[1]
Musculoskeletal and connective tissue disorders	Myalgia[1]
Reproductive system and breast disorders	Sexual dysfunction[1], decreased libido[1]
General disorders and administration site conditions	Asthenia[1,2]
Investigations	Liver function tests (LFT) abnormal[2]

[1] adverse reactions observed with timolol
[2] adverse reactions observed with bimatoprost

Adverse reactions reported in phosphate containing eye drops

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.

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: Ophthalmologicals – antiglaucoma preparations and miotics - beta-blocking agents – timolol, combinations – 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 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 (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 $AUC_{0-24hrs}$ 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 l/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 l/hr/kg.

Characteristics in elderly patients

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 single-dose container is removed from the pouch use within 7 days. All single-dose containers should be kept in the pouch and discarded after 10 days from the first opening of the pouch.

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 and place the pouch back in carton 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:
- Carton containing 5 single-dose containers in an aluminium foil pouch.
- Carton containing 30 or 90 single-dose containers in three or nine aluminium foil pouches respectively. Each pouch contains 10 single-dose containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

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

Detailed information on this medicinal product is available on the website of the European Medicines Agency web site: https://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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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 4 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

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ganfort

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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 4 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

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ganfort

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

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

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

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

AbbVie (as logo)

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 container immediately after use.
Once the container is removed from the pouch use within 7 days.
All containers should be kept in the pouch and carton to protect from light and moisture and discarded 10 days after first opening the pouch.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

For single use only

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

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. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Ocular use
5 single-dose containers.
For single use only.
Read the package leaflet before use.
Once the container is removed from the pouch use within 7 days.
All containers should be kept in the pouch and carton to protect from light and moisture and discarded 10 days after first opening the pouch.
Discard the opened container immediately after use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON CONTAINING 30 or 90 SINGLE-DOSE CONTAINERS (PROVIDED IN 3 or 9 POUCHES, EACH CONTAINING 10 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
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

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/340/004
EU/1/06/340/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

For single use only

16. INFORMATION IN BRAILLE

ganfort single-dose

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

POUCH CONTAINING STRIP OF 10 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. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Ocular use
10 single-dose containers.
For single use only.
Read the package leaflet before use.
Once the container is removed from the pouch use within 7 days.
All containers should be kept in the pouch and carton to protect from light and moisture and discarded 10 days after first opening the pouch.
Discard the opened container immediately after use.

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 patient

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

- if you are allergic to bimatoprost, timolol, beta-blockers or any of the other ingredients of this medicine (listed in section 6)
- if you have now or have had in past respiratory problems such as asthma and/or severe chronic obstructive pulmonary disease (lung disease which may cause wheeziness, difficulty in breathing and/ or long-standing cough) or other types of breathing problems
- 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 or 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. GANFORT may cause hair growth when in contact with the skin surface.

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

Other medicines and GANFORT
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

GANFORT can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma. 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.

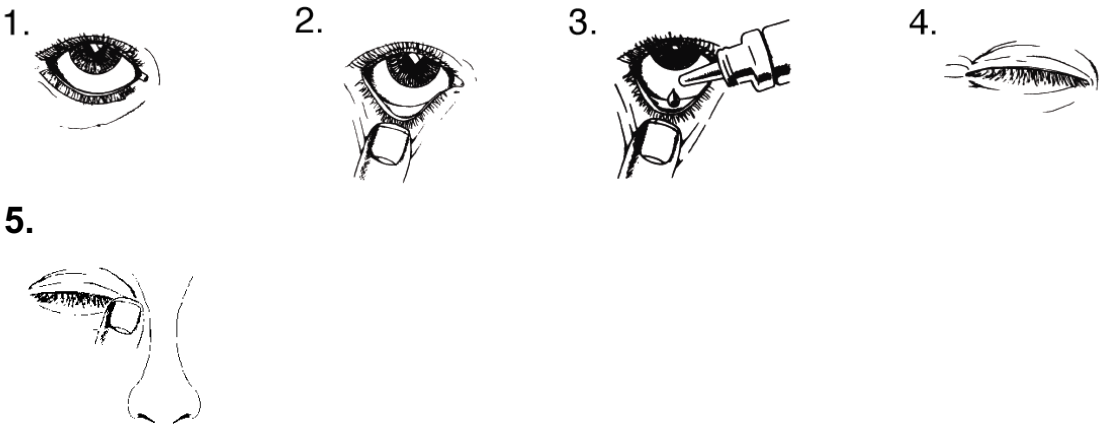
GANFORT contains benzalkonium chloride
Ganfort contains a preservative called benzalkonium chloride.
This medicine contains 0.15 mg benzalkonium chloride in each 3 ml of solution which is equivalent to 0.05 mg/ml.
Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. You should remove contact lenses before using this medicine and put them back 15 minutes afterwards.
Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.

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.



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 following side effects may be seen with GANFORT (multi-dose and/or single-dose):

Very common: may affect more than 1 in 10 people
Affecting the eye
redness.

Common: may affect up to 1 in 10 people
Affecting the eye
burning, itching, stinging, irritation of the conjunctiva (see-through layer of the eye), 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, hair growing around the eye, darkening of the eyelids, darker skin colour around the eyes, longer eyelashes, eye irritation, watery eyes, swollen eyelids, reduced vision.

Affecting other parts of the body
runny nose, headache.

Uncommon: may affect up to 1 in 100 people
Affecting the eye
abnormal sensation in the eye, iris inflammation, swollen conjunctiva (see-through layer of the eye), painful eyelids, tired eyes, in-growing eyelashes, darkening of iris colour, eyes appear sunken, eyelid drooping, eyelid shrinking (moving away from the surface of the eye leading to incomplete closure of the eyelids), skin tightness of the eyelids, darkening of eyelashes.

Affecting other parts of the body
shortness of breath.

Not known: frequency cannot be estimated from the available data
Affecting the eye
cystoid macular oedema (swelling of the retina within the eye leading to worsening vision), eye swelling, blurred vision, ocular discomfort.

Affecting other parts of the body
difficulty breathing / wheezing, symptoms of allergic reaction (swelling, redness of the eye and rash of the skin), changes in your taste sensation, dizziness, slowing of heart rate, high blood pressure, difficulty sleeping, nightmare, asthma, hair loss, skin discolouration (periocular), tiredness.

Additional side effects have been seen in patients using eye drops containing timolol or bimatoprost 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 bimatoprost and timolol when used for treating eye conditions:

- Severe allergic reactions with swelling and difficulty breathing which could be life-threatening
- Low blood sugar
- Depression; memory loss; hallucination
- Fainting; stroke; decreased blood flow to the brain; worsening of myasthenia gravis (increased muscle weakness); tingling sensation

- 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, bleeding in the back of the eye (retinal bleeding), inflammation within the eye, increased blinking
- Heart failure; irregularity or stopping of the heartbeat; 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, worsening of asthma, worsening of the lung disease called chronic obstructive pulmonary disease (COPD)
- Diarrhoea; stomach pain; feeling and being sick; indigestion; dry mouth
- Red scaly patches on skin; skin rash
- Muscle pain
- Reduced sexual urge; sexual dysfunction
- Weakness
- An increase in blood test results that show how your liver is working

Other side effects reported with eye drops containing phosphates
This medicine contains 2.85 mg phosphates in each 3 ml of solution which is equivalent to 0.95 mg/ml. If you suffer from severe damage to the clear layer at the front of the eye (the cornea), phosphates may cause in very rare cases cloudy patches on the cornea due to calcium build-up during treatment.

Reporting of side effects
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 this medicine out of the sight and reach of children.

Do not use this medicine 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 (see section 2).

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.

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AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

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.

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This leaflet was last revised in

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

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

Package leaflet: Information for the patient

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

- if you are allergic to bimatoprost, timolol, beta-blockers or any of the other ingredients of this medicine single-dose (listed in section 6)
- if you have now or have had in past respiratory problems such as asthma and/or severe chronic obstructive pulmonary disease (lung disease which may cause wheeziness, difficulty in breathing and/ or long-standing cough) or other types of breathing problems
- 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. GANFORT single-dose may cause hair growth when in contact with the skin surface.

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

Other medicines and GANFORT
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

GANFORT single-dose can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma. 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.

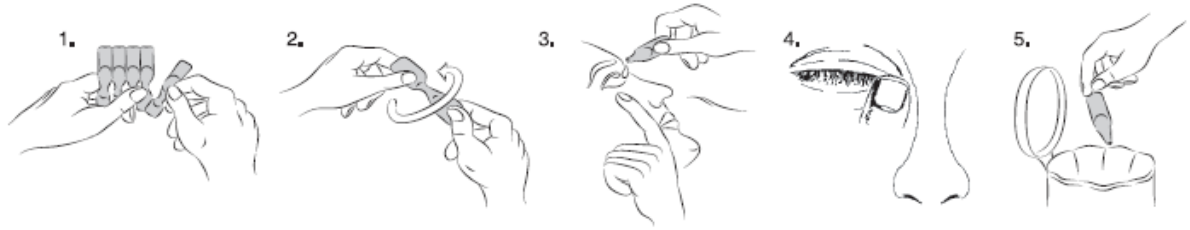
Driving and using machines
GANFORT single-dose may cause blurred vision in some patients. Do not drive or use machines until the symptoms have cleared.

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 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
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
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 following side effects may be seen with GANFORT (multi-dose and/or single-dose):

Very common: may affect more than 1 in 10 people
Affecting the eye
redness.

Common: may affect up to 1 in 10 people
Affecting the eye
burning, itching, stinging, irritation of the conjunctiva (see-through layer of the eye), 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, hair growing around the eye, darkening of the eyelids, darker skin colour around the eyes, longer eyelashes, eye irritation, watery eyes, swollen eyelids, reduced vision.

Affecting other parts of the body
runny nose, headache.

Uncommon: may affect up to 1 in 100 people
Affecting the eye
abnormal sensation in the eye, iris inflammation, swollen conjunctiva (see-through layer of the eye), painful eyelids, tired eyes, in-growing eyelashes, darkening of iris colour, eyes appear sunken, eyelid drooping, eyelid shrinking (moving away from the surface of the eye leading to incomplete closure of the eyelids), skin tightness of the eyelids, darkening of eyelashes.

Affecting other parts of the body
shortness of breath.

Not known: frequency cannot be estimated from the available data
Affecting the eye
cystoid macular oedema (swelling of the retina within the eye leading to worsening vision), eye swelling, blurred vision, ocular discomfort.

Affecting other parts of the body
difficulty breathing / wheezing, symptoms of allergic reaction (swelling, redness of the eye and rash of the skin), changes in your taste sensation, dizziness, slowing of heart rate, high blood pressure, difficulty sleeping, nightmare, asthma, hair loss, skin discolouration (periocular), tiredness.

Additional side effects have been seen in patients using eye drops containing timolol or bimatoprost 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 bimatoprost and timolol when used for treating eye conditions:

- Severe allergic reactions with swelling and difficulty breathing which could be life-threatening
- Low blood sugar
- Depression; memory loss; hallucination
- Fainting; stroke; decreased blood flow to the brain; worsening of myasthenia gravis (increased muscle weakness); tingling sensation
- 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, bleeding in the back of the eye (retinal bleeding), inflammation within the eye, increased blinking
- Heart failure; irregularity or stopping of the heartbeat; 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, worsening of asthma, worsening of the lung disease called chronic obstructive pulmonary disease (COPD)
- Diarrhoea; stomach pain; feeling and being sick; indigestion; dry mouth
- Red scaly patches on skin; skin rash
- Muscle pain
- Reduced sexual urge; sexual dysfunction
- Weakness
- An increase in blood test results that show how your liver is working

Other side effects reported with eye drops containing phosphates
This medicine contains 0.38 mg phosphates in each 0.4 ml of solution which is equivalent to 0.95 mg/ml. If you suffer from severe damage to the clear layer at the front of the eye (the cornea), phosphates may cause in very rare cases cloudy patches on the cornea due to calcium build-up during treatment.

Reporting of side effects
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 this medicine single-dose out of the sight and reach of children.

Do not use this medicine single-dose after the expiry date which is stated on the single-dose container and the carton after EXP. 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 medicine does not require any special temperature storage conditions. Keep the single-dose containers in the pouch and place the pouch back in carton in order to protect from light and moisture. Once the single-dose container is removed from the pouch use within 7 days. All single-dose containers should be kept in the pouch and discarded after 10 days from the first opening of the pouch.

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.

Pack contains 1 foil pouch containing 5 single-dose containers in a carton.

Packs contain 3 or 9 foil pouches, each containing 10 single-dose containers, for a total of 30 or 90 single-dose containers in a carton, respectively.

Not all pack sizes may be marketed.

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

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