SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

GANFORT 0,3 mg/ml + 5 mg/ml eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains bimatoprost 0,3 mg and timolol maleate equivalent to 5 mg timolol

Excipient with known effect

Contains benzalkonium chloride 0,005 % w/v as a preservative

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless to slightly yellow eye drop solution, practically free from particles.

GANFORT has an osmolality of 270 – 310 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to a topical beta-blocker or prostaglandin analogue(s) given alone.

4.2 Posology and method of administration

Posology

Recommended dosage in adults (including the 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.

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.

Special populations

Use in 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

GANFORT has only been studied in adults and therefore its use is not recommended in children or adolescents

Method of administration

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

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced.

4.3 Contraindications

- Hypersensitivity to the bimatoprost, timolol or to any of the excipients in GANFORT 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 a pace-maker, overt cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

The components of GANFORT may be absorbed systemically. 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. To reduce systemic absorption, see section 4.2.

Cardiac disorders

In patients with cardiovascular diseases (e.g. coronary artery disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers, as in GANFORT should be

critically assessed and therapy with other active substances should be considered.

GANFORT should be used with caution in patients with cardiovascular disease (e.g. coronary heart disease, Prinzmetal's angina, first degree heart block and cardiac failure) and hypotension. Patients with cardiovascular diseases should be monitored for signs of deterioration of these diseases, and of adverse reactions.

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

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

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

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
Timolol, as in GANFORT should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) as beta-blockers may mask the signs or symptoms of acute hypoglycaemia.

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases
Timolol, as in GANFORT 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, as in GANFORT, is given to patients already receiving a systemic

beta-blocking medicine. Caution should be exercised when used concomitantly with systemic beta-adrenergic blocking medicines. The response of these patients should be closely observed. The use of two beta-adrenergic blocking medicines is not recommended (see section 4.5).

Anaphylactic reactions

While taking timolol, as in GANFORT, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to a repeated challenge with such allergens and unresponsive to the usual dose of (epinephrine) adrenaline used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy such as timolol, after filtration procedures.

Surgical anaesthesia

Ophthalmic beta-blockers may impair compensatory tachycardia and increase risk of hypotension when used in conjunction with anaesthetics. Timolol, such as in GANFORT, may block systemic beta-agonist effects e.g. of epinephrine (adrenaline). The anaesthesiologist should be informed when the patient is receiving GANFORT.

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, as in GANFORT, on liver function.

Ocular

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

Macular oedema, including cystoid macular oedema has been reported during treatment with GANFORT. GANFORT should be used with caution in aphakic patients, 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 and may also be absorbed by soft contact lenses. Contact lenses must be removed prior to application, with at least a 15-minutes 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.

As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations cannot be excluded, regular ophthalmological examination is required.

Caution should be exercised in the use of benzalkonium chloride preserved topical medicines over an extended period, in patients with extensive ocular surface disease.

Other conditions

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

angle glaucoma.

In studies in patients with glaucoma or ocular hypertension with bimatoprost ophthalmic solution 0,03 %, it has been shown that more frequent exposure of the eye to more than one dose of bimatoprost (as in GANFORT) 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 medicines and other forms of interaction

No specific interaction studies have been performed with GANFORT.

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

There is a potential for additive effects resulting in hypotension and/or marked bradycardia, when an ophthalmic beta-blocker solution, such as GANFORT, is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking medicines, anti-dysrhythmics (including amiodarone), digoxin or parasympathomimetics and other anti-hypertensives.

Timolol as in GANFORT can mask the signs and symptoms of and the body's reaction to hypoglycaemia (see section 4.8).

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

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

Mydriasis resulting from concomitant use of ophthalmic beta-blockers such as in timolol and adrenaline (epinephrine) has been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of GANFORT in pregnant women.

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.

Breastfeeding

Timolol is excreted in breastmilk. It is not known if bimatoprost is excreted in human breastmilk. Women on GANFORT should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

Transient blurred vision may occur at installation, therefore the patient should wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported side effect was conjunctival hyperaemia in approximately 26 % of patients and led to discontinuation in 1,5 % of patients.

Tabulated summery of adverse reactions

Table 1 presents the adverse reactions that have been reported during clinical studies with all GANFORT formulations (GANFORT multi-dose and bimatoprost/timolol single-dose formulation) (within each frequency grouping, adverse reactions are presented in order of decreasing seriousness) or in the post-marketing period.

The frequency is defined as follows: Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥ 1/1 000 to < 1/100); Rare (≥ 1/10 000 to < 1/1 000); Very Rare (< 1/10 000); Not known (cannot be estimated from available data).

Table 1

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, growth of eyelashes
	Common	Superficial punctate keratitis, corneal erosion[2], burning sensation[2], conjunctival irritation[1], eye pruritus, stinging sensation in the eye[2], foreign body sensation, dry eye, eyelid erythema, eye pain, photophobia, eye discharge, visual disturbance[2], eyelid pruritus, visual acuity worsened[2], blepharitis[2], eyelid oedema, eye irritation, lacrimation increased
	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], epiphora
	Not known	Cystoid macular oedema[2], eye swelling, blurred vision[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	Common	Blepharal pigmentation[2], hirsutism[2], periocular skin hyperpigmentation

disorders		
	Not known	Alopecia, periocular skin discolouration
General disorders and administration site conditions	Not known	Fatigue

[1] Adverse reactions only observed with bimatoprost/timolol single-dose formulation

[2] Adverse reactions only observed with Ganfort multi-dose formulation

GANFORT (bimatoprost/timolol) is absorbed into the systemic circulation. Absorption of timolol may cause similar undesirable effects as seen with systemic beta-blocking medicines. To reduce the systemic absorption, see section 4.2.

Additional side effects that have been seen with one of the components and may potentially occur also with GANFORT are listed below in Table 2.

Table 2

System Organ Class	**Adverse reaction**
Immune system disorders	Systemic allergic reactions including anaphylaxis[1], urticarial, localised and generalised rash[1], pruritus[1]
Metabolism and nutrition disorders	Hypoglycaemia[1]
Psychiatric disorders	Behavioural changes and psychic disturbances including depression[1], memory loss[1], hallucination[1], anxiety[1], disorientation[1], confusion[1], nervousness[1], somnolence[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[1] (see section 4.4), keratitis[1], blepharospasm[2], retinal haemorrhage[2], uveitis[2], refractive changes (due to withdrawal of miotic therapy in some cases)[1], pseudopemphigoid[1], signs and symptoms of ocular irritation including conjunctivitis[1], allergic conjunctivitis[2]
Ear and labyrinth disorders	Tinnitus[1]
Cardiac disorders	Atrioventricular block[1], cardiac arrest[1], dysrhythmia[1], cardiac

	failure[1], congestive heart failure[1], chest pain[1], palpitations[1], oedema[1], pulmonary oedema[1], worsening of angina pectoris[1]
Vascular disorders	Hypotension[1], Raynaud's phenomenon[1], cold hands and feet[1], claudication[1]
Respiratory, thoracic and mediastinal disorders	Asthma exacerbation[2], COPD exacerbation[2], cough[1], nasal congestion[1], respiratory failure[1], upper respiratory infection[1]
Gastrointestinal disorders	Nausea[1,2], diarrhoea[1], dyspepsia[1], dry mouth[1], abdominal pain[1], vomiting[1], anorexia[1]
Skin and subcutaneous tissue disorders	Psoriasiform rash[1], exacerbation of psoriasis[1], skin rash[1], abnormal hair growth[2]
Musculoskeletal and connective tissue disorders	Myalgia[1], systemic lupus erythematosus[1]
Reproductive system and breast disorders	Sexual dysfunction[1], decreased libido[1], Peyronie's disease[1], retroperitoneal fibrosis[1]
General disorders and administration site conditions	Asthenia[1,2], peripheral oedema[2]
Investigations	Liver function tests (LFT) abnormal[2]
Infection and infestations	Infection (primary colds and upper respiratory symptoms) [1,2]

[1] Adverse reactions observed with timolol

[2] Adverse reactions observed with bimatoprost

Description of selected adverse reactions

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

In case of a side effect, please contact MEAPV@abbvie.com

4.9 Overdose

In overdose, side effects may be exacerbated and exaggerated (see section 4.8). Symptoms of systemic timolol overdose include: bradycardia, hypotension, bronchospasm, headache, dizziness, shortness of breath, and cardiac arrest. Timolol does not dialyse readily.
If overdose occurs treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacological classification: A. 15.4 Ophthalmological preparations. Others

The two active substances, bimatoprost and timolol maleate, 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. The onset of action is rapid.

Bimatoprost is an ocular hypotensive agent. 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 biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. Bimatoprost reduces intraocular pressure 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. 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

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

5.2 Pharmacokinetic properties

Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to a combination 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-months 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 bimatoprost 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 substance in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-de-ethylation 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 from ocular dosing for both elderly and young subjects remained very low. 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 0,5 % eye drop 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 proteins.

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
Do not use more than 28 days after first opening

6.4 Special precautions for storage

Store at or below 25 °C.
Keep bottle tightly closed when not in use. See section 6.3.

6.5 Nature and contents of container

5 ml white opaque low-density polyethylene bottles with a high impact polystyrene blue screw cap, packed into an outer carton containing one or three bottles. Each bottle is filled with 3 ml solution. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

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