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## **SCHEDULING STATUS**

Schedule 4

## **PROPRIETARY NAME AND DOSAGE FORM**

GANFORT Eye Drops

## **COMPOSITION**

Each ml contains: Bimatoprost 0,3 mg and timolol maleate equivalent to 5 mg timolol

Preservative: Benzalkonium chloride 0,005 % w/v.

Inactives: 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 level.

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

## **PHARMACOLOGICAL CLASSIFICATION**

A. 15.4 Ophthalmic Preparations. Other

## **PHARMACOLOGICAL ACTION**

### **Pharmacodynamic Properties**

#### *Mechanism of action*

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 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. 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.

### **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  $AUC_{0-24hrs}$  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  $AUC_{0-24hrs}$  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 0,5 % eye drop solution in humans undergoing cataract

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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.

### **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 analogues given alone.

### **CONTRA-INDICATIONS**

Hypersensitivity to the active substances or to any of the excipients.

Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.

Sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock.

### **WARNINGS AND SPECIAL PRECAUTIONS**

GANFORT contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of GANFORT and may be reinserted 15 minutes following administration.

Benzalkonium chloride is known to discolour soft contact lenses. Contact with soft contact lenses must be avoided.

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 medication over an extended period in patients with extensive ocular surface disease.

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

GANFORT may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed.

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Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-blockers may occur.

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 a history of cardiovascular disease should be monitored for signs of deterioration of these diseases.

Cardiac failure should be adequately controlled before beginning GANFORT therapy. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked.

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 or moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Beta-blockers may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and hypotension.

Patients with severe peripheral circulatory disturbance/disorders (i.e. Raynaud's phenomenon) should be treated with caution.

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

Timolol, as in GANFORT may induce dryness of the eyes. Patients with corneal diseases should be treated with caution.

Caution should be exercised when used concomitantly with systemic beta-adrenergic blocking agents because of the potential for additive effects on systemic beta-blockade. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking medicines is not recommended.

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual dose of epinephrine (adrenaline) used to treat anaphylactic reactions.

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

Ophthalmic beta-blockers may impair compensatory tachycardia and increase risk of hypotension when used in conjunction with anaesthetics. The anaesthetist must be informed if the patient is using GANFORT.

GANFORT has not been studied in patients with hepatic or renal impairment. Caution should be used treating such patients.

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

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 bimatoprost and 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 only 0,2 %. After 12 months treatment with bimatoprost eye drops alone, the incidence was 1,5 % and did not increase following 3 years treatment.

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.

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

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### **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 installation, the patient should wait until the vision clears before driving or using machinery.

### **INTERACTIONS**

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 eye drops containing timolol are administered concomitantly with oral calcium channel blockers or beta-blocking agents, anti-dysrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics and other anti-hypertensives.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see WARNINGS AND SPECIAL PRECAUTIONS).

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

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

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

### **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.

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## **Lactation**

Timolol is excreted in breast milk. It is not known if bimatoprost is excreted in human breast milk. GANFORT should not be used by breast-feeding women.

## **DOSAGE AND DIRECTIONS FOR USE**

### *Recommended dosage in adults (including the elderly)*

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

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.

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

### *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.

### *Use in children and adolescents*

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

## **SIDE EFFECTS**

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

The following side effects were reported during clinical trials with GANFORT (within each frequency grouping, undesirable effects are presented in order of decreasing seriousness):

### ***Nervous system disorders***

*Uncommon (>1/1000, ≤1/100):* Headache

### ***Eye disorders***

*Very common (>1/10):* Conjunctival hyperaemia, growth of eyelashes

*Common (>1/100, ≤1/10):* Superficial punctate keratitis, corneal erosion, burning sensation, eye pruritus, stinging sensation in the eye, foreign body sensation, eye dryness, eyelid erythema, eye pain, photophobia, eye discharge, visual disturbance, eyelid pruritus, blepharal pigmentation

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

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***Respiratory, thoracic and mediastinal disorders***

*Uncommon (>1/1000, ≤1/100):* Rhinitis

***Skin and subcutaneous tissue disorders***

*Uncommon (>1/1000, ≤1/100):* Hirsutism

**Post-marketing Experience**

The following adverse reactions have been identified during post-marketing use of GANFORT in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

***Cardiac disorders***

Bradycardia

***Eye disorders***

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

***General disorders and administration site conditions***

Fatigue

***Immune system disorders***

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

***Nervous system disorders***

Dizziness, dysgeusia

***Psychiatric disorders***

Insomnia, nightmare

***Respiratory, thoracic and mediastinal disorders***

Asthma, dyspnoea

***Skin and subcutaneous tissue disorders***

Alopecia, periocular skin hyperpigmentation, periocular skin discolouration

***Vascular disorders***

Hypertension



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Additional side effects that have been seen with one of the components and may potentially occur also with GANFORT:

### **Bimatoprost**

*Infection and infestations:* Infection (primarily colds and upper respiratory symptoms).

*Eye disorders:* Allergic conjunctivitis, cataract, eyelash darkening, blepharospasm, retinal haemorrhage, uveitis.

*Skin and subcutaneous tissue disorders*

Abnormal hair growth

*Gastrointestinal disorders:* Nausea

*General disorders and administration site condition:* Asthenia, peripheral oedema.

*Investigations:* Liver function tests (LFT) abnormal.

### **Timolol**

*Psychiatric disorders:* Behavioural changes and psychic disturbances including anxiety, confusion, depression, disorientation, hallucinations, nervousness, somnolence

*Nervous system disorders:* Memory loss, increase in signs and symptoms of myasthenia gravis, paraesthesia, cerebral ischaemia

*Eye disorders:* Decreased corneal sensitivity, diplopia, ptosis, choroidal detachment (following filtration surgery), refractive changes (due to withdrawal of miotic therapy in some cases), keratitis, pseudophthalmos, signs and symptoms of ocular irritation including conjunctivitis

*Ear and labyrinth disorders:* Tinnitus

*Cardiac disorders:* Heart block, cardiac arrest, dysrhythmia, syncope, cardiac failure, congestive heart failure, atrioventricular block, chest pain, oedema, palpitations, pulmonary oedema, worsening of angina pectoris

*Vascular disorders:* Hypotension, cerebrovascular accident, claudication, Raynaud's phenomenon, cold hands and feet

*Respiratory, thoracic and mediastinal disorders:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), cough, nasal congestion, respiratory failure, upper respiratory infection

*Gastrointestinal disorders:* Nausea, diarrhoea, dyspepsia, dry mouth, abdominal pain, anorexia, vomiting

*General disorders and administration site condition:* Asthenia

*Immune system disorders:* Systemic allergic reactions including anaphylaxis

*Endocrine system disorders:* Hypoglycaemia (in diabetic patients)

*Reproductive system and breast disorders:* Decreased libido, Peyronie's disease, retroperitoneal fibrosis, sexual dysfunction

*Skin and subcutaneous tissue disorders:* Psoriasiform rash, exacerbation of psoriasis, skin rash

*Musculoskeletal and connective tissue disorders:* Systemic lupus erythematosus, myalgia

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## **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

No case of overdose has been reported, and is unlikely to occur after ocular administration. Symptoms of systemic timolol overdose are: 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.

## **IDENTIFICATION**

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

## **PRESENTATION**

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.

## **STORAGE INSTRUCTIONS**

Store below 25 °C. Do not use more than 30 days after opening.

Keep bottle tightly closed when not in use.

KEEP OUT OF REACH OF CHILDREN.

## **REGISTRATION NUMBER**

42/15.4/0127

## **NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION**

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## **DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION**

Date of registration: 09 October 2009

Date of most recently revised Professional Information as approved by the Authority: 09 October 2009