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.
Excipients: Sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate and purified water.
GANFORT has an osmolality of 270 – 310 mOsm/kg.

PHARMACOLOGICAL CLASSIFICATION
A. 15.4 Ophthalmic Preparations. Other

PHARMACOLOGICAL ACTION
Pharmacodynamic Properties
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.

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.

Summary of Clinical Studies
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.

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.

CONTRAINDICATIONS
- Hypersensitivity to the bimatoprost, timolol or to any of the excipients in GANFORT.
- 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.

WARNINGS AND SPECIAL PRECAUTIONS
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.

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.

GANFORT should be used with caution in patients with active intraocular inflammation (e.g.

uveitis) because the inflammation may be exacerbated.

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 DOSAGE AND DIRECTIONS FOR USE.

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.

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.

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

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.

Beta-blockers may also mask the signs of hyperthyroidism.

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

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.

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

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 INTERACTIONS).

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 has been reported with 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.

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.

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.

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.

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.

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.

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 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 SIDE EFFECTS).

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.

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.

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

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 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.

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.

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, iris hyperpigmentation, deepening of eyelid sulcus (enophthalmos)

Respiratory, thoracic and mediastinal disorders
Uncommon (≥1/1000, <1/100): Rhinitis

Skin and subcutaneous tissue disorders
Common (≥1/100, <1/10): Periocular skin hyperpigmentation
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, 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 discolouration

Vascular disorders
Hypertension

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

Bimatoprost
Infection and infestations: Infection (primary colds and upper respiratory symptoms)
Eye disorders: Allergic conjunctivitis, 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
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 DOSAGE AND DIRECTIONS FOR USE.

Additional adverse reactions that have been seen with ophthalmic beta-blockers and may potentially also occur with GANFORT are listed below:
Infection and infestations: Infection (primarily colds and upper respiratory symptoms)
Immune system disorders: Systemic allergic reactions including urticarial, localised and generalised rash, pruritus, anaphylaxis
Endocrine system disorders: Hypoglycaemia (in diabetic patients)
Psychiatric disorders: Behavioural changes and psychic disturbances including anxiety, confusion, depression, disorientation, hallucinations, nervousness, somnolence
Nervous system disorders: Syncope, cerebrovascular accident, increase in signs and symptoms

of myasthenia gravis, paraesthesia, cerebral ischaemia
Eye disorders: Decreased corneal sensitivity, diplopia, ptosis, choroidal detachment (following filtration surgery), refractive changes (due to withdrawal of miotic therapy in some cases), keratitis, pseudopemphigoid, signs and symptoms of ocular irritation including conjunctivitis
Ear and labyrinth disorders: Tinnitus
Cardiac disorders: Atrioventricular block, cardiac arrest, dysrhythmia, cardiac failure, congestive heart failure, chest pain, palpitations, oedema, pulmonary oedema, worsening of angina pectoris
Vascular disorders: Hypotension, 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
Skin and subcutaneous tissue disorders: Psoriasiform rash, exacerbation of psoriasis, skin rash
Musculoskeletal and connective tissue disorders: Myalgia, systemic lupus erythematosus
Reproductive system and breast disorders: Sexual dysfunction, decreased libido, Peyronie's disease, retroperitoneal fibrosis
General disorders and administration site conditions: Asthenia

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In overdose, side-effects may be exacerbated and exaggerated (see SIDE EFFECTS). 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.

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 at or below 25 °C. Do not use more than 28 days after opening.
Keep bottle tightly closed when not in use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

42/15.4/0127

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