## 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
### Pharmacodynamics
*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.

### Pharmacokinetics
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 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 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.

**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**
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.

**INTERACTIONS**
No interaction studies have been performed.

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-arrhythmics, digitalis glycosides or parasympathomimetics.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see “Side Effects and Special Precautions”).

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

## 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 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 AND SPECIAL PRECAUTIONS

### 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 punctuate keratitis, corneal erosion, burning sensation, eye pruritus, stinging sensation in the eye, foreign body sensation, eye dryness, eyelid erythema, eye pain, photophobia, eye discharge, visual disturbance, eyelid pruritus.

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

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

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

***Skin and subcutaneous tissue disorders***

*Common (>1/100, <1/10)*: Blepharal pigmentation

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

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).

*Nervous system disorders:* Dizziness

*Eye disorders:* Allergic conjunctivitis, cataract, eyelash darkening, increased iris pigmentation, blepharospasm, cystoid macular oedema, eyelid retraction, retinal haemorrhage, uveitis.

*Vascular disorders:* Hypertension.

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

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

**Timolol**

*Psychiatric disorders:* Insomnia, nightmares, decreased libido

*Nervous system disorders:* Dizziness, 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.

*Ear and labyrinth disorders:* Tinnitus.

*Cardiac disorders:* Heart block, cardiac arrest, arrhythmia, syncope, bradycardia, cardiac

failure, congestive heart failure.
*Vascular disorders:* Hypotension, cerebrovascular accident, claudication, Raynaud's phenomenon, cold hands and feet, palpitation.
*Respiratory, thoracic and mediastinal disorders:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease) dyspnoea, cough.
*Gastrointestinal disorders:* Nausea, diarrhoea, dyspepsia, dry mouth.
*Skin and subcutaneous tissue disorders:* Alopecia, psoriasiform rash or exacerbation of psoriasis.
*Musculoskeletal and connective tissue disorders*: Systemic lupus erythematosus.
*Renal and urinary disorders*: Peyronie's disease
*General disorders and administration site conditions*: Oedema, chest pain, fatigue

**Special precautions**
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 and pulmonary adverse reactions as seen with systemic beta-blockers may occur.

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.

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

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 of symptoms of acute hypoglycaemia.

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 adrenaline used to treat anaphylactic reactions.

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.

Cystoid macular oedema has not been reported with GANFORT, however, it has been uncommonly reported (> 0,1 % to < 1 %) following treatment with bimatoprost. Therefore, GANFORT should be used with caution in patients with known risk factors for macular oedema (e.g. aphakic patients, pseudophakic patients with a torn posterior lens capsule).

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

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.

**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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