GANFORT® eye drops, solution

Bimatoprost 0.3 mg/mL and timolol 5.0 mg/mL

DESCRIPTION

Each mL contains: 0.3 mg bimatoprost and 5 mg timolol equivalent to 6.8 mg of timolol maleate, benzalkonium chloride as preservative, sodium chloride, dibasic sodium phosphate heptahydrate, citric acid monohydrate, hydrochloric acid or sodium hydroxide (to adjust pH), purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group:

Ophthalmological – beta-blocking agents – timolol, combinations

ATC code: SO1ED 51

Mechanism of action:

GANFORT® consists of two active substances: bimatoprost and timolol maleate. 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 agent, which selectively mimics the effects of naturally occuring prostamide $F_{2\alpha}$. It is structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), except that it is electrochemically neutral by virtue of the ethanolamide group at position C1. It is pharmacologically unique and acts through an identified prostamide receptor. The prostamide receptor has been structurally identified as a heterodimer of an alternative mRNA splicing variant of the prostanoid FP receptor (alt.FP4) and the FP wild type.

The efficacy of bimatoprost may be related to a dual mechanism of action on aqueous humour outflow that involves both the uveoscleral and the trabecular meshwork/Schlemm's canal pathways. Studies in living human subjects, human eyes in organ culture, and studies on human ciliary smooth muscle cells, trabecular meshwork cells, and endothelial cells of Schlemm's canal all indicate that bimatoprost stimulates both trabecular and uveoscleral outflow pathways.

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).

Morning dosing of GANFORT® is currently recommended based on the clinical studies conducted by Allergan. However, if necessary for patient compliance, an evening dosing may be considered. Bimatoprost studies show comparable IOP control regardless of morning or evening dosing.

Pharmacokinetic properties

GANFORT®:

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 Cmax 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 1/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 1/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 a 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.

INDICATIONS AND USAGE

Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

CONTRAINDICATIONS

• 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, sick sinus syndrome, sino-atrial nodal block, second or third degree atrioventricular block not controlled with a pacemaker; overt cardiac failure, cardiogenic shock.

PRECAUTIONS

Like other topically applied ophthalmic agents, 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 disorders: Although rare, cardiac reactions have been reported, including death due to cardiac failure. 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.

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 diseases should be watched for signs of deterioration of these diseases.

Respiratory Disorder: Although rare, respiratory reactions have been reported, including death, due to bronchospasm. GANFORT® should be administered with caution in patients with mild or moderate chronic obstructive pulmonary disease.

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

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

Anaphylaxis: 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.

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 0.2%. After 12 months treatment with bimatoprost eye drops alone, the incidence was 1.5% and did not increase following 3 years treatment.

GANFORT® has been reported to cause changes to pigmented tissues. The most frequently reported pigmentary changes have been increased pigmentation of periocular skin and eyelash darkening. Periorbital tissue pigmentation has been reported to be reversible in some patients.

There is the 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 to avoid it running onto the cheek or other skin areas.

In bimatoprost ophthalmic solution 0.03% studies 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 bimatoprost ophthalmic solutions with other prostaglandin analogs should be monitored for changes to their intraocular pressure.

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

Macular edema, including cystoid macular oedema has not been reported during treatment 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 (intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy), in aphakic patients, or in pseudophakic patients with a torn posterior lens capsule.

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

Corneal Disease: Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Choroidal detachment: Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Other beta-blocking agents: 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 agents is not recommended.

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline.

Surgical anesthesia: Ophthalmic beta-blockers may impair compensatory tachycardia and increase risk of hypotension when used in conjunction with anesthetics. The anesthetist must be informed if the patient is using GANFORT®

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.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to avoid eye injury and contamination of eye drops.

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.

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

Drug Interactions:

No interaction studies have been performed.

Patients who are receiving a systemic (e.g. oral or intravenous) beta-adrenergic blocking agent and GANFORT® should be observed for potential additive effects of beta-blockade, 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, guanethidine, or beta-blocking agents, anti-arrhythmics (including amiodarone), digitalis glycosides or

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.

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

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

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.

Pregnancy and lactation

Pregnancy

There are no adequate data from the use of GANFORT® in pregnant women. GANFORT® should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Bimatoprost

No adequate clinical data in exposed pregnancies are available. Animal studies have shown reproductive toxicity at high maternotoxic doses.

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.

Consequently, GANFORT® should not be used during pregnancy unless clearly necessary.

Lactation

Timolol is excreted in breast milk. 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.

Preclinical safety data:

GANFORT®:

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.

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 machinery.

ADVERSE EVENTS

No new adverse drug reactions (ADRs) specific for GANFORT® have been observed in clinical studies. The ADRs also include those earlier reported for either of the single active substances bimatoprost and timolol.

The majority of ADRs were ocular, mild in severity and none were serious. Based on 12-month clinical data, the most commonly reported ADR 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.

The following ADRs 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 adverse events that have been seen with one of the components and may potentially occur also with GANFORT®:

Bimatoprost

Infections and infestations: infection (primarily colds and upper respiratory symptoms).

Eye disorders: allergic conjunctivitis, cataract, eyelash darkening, blepharospasm, eyelid retraction, retinal haemorrhage, uveitis, periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos and eyelid retraction.

General disorders and administration site condition: asthenia, peripheral oedema.

Investigations: liver function tests (LFT) abnormal.

Timolol

Psychiatric disorders: behavioral changes and psychic disturbances including anxiety, confusion, depression, disorientation, hallucinations, nervousness, somnolence, memory loss.

Nervous system disorders: increase in signs and symptoms of myasthenia gravis, paresthaesia, cerebral ischaemia, cerebrovascular accident.

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

Ear and labyrinth disorders: tinnitus.

Cardiac disorders: heart block, cardiac arrest, arrhythmia, atrioventricular block, syncope, cardiac failure, congestive heart failure, pulmonary edema, worsening of angina pectoris, palpitations, chest pain, edema .

Vascular disorders: hypotension, claudication, Raynaud's phenomenon, cold hands and feet,.

Respiratory, thoracic and mediastinal disorders: bronchospasm (predominantly in patients with preexisting bronchospastic disease) cough, nasal congestion, respiratory failure, upper respiratory infection.

Gastrointestinal disorders: nausea, abdominal pain, anorexia, diarrhoea, dyspepsia, dry mouth, vomiting.

Skin and subcutaneous tissue disorders: psoriasiform rash, exacerbation of psoriasis, skin rash.

Musculoskeletal and connective tissue disorders: systemic lupus erythematosus.

Renal and urinary disorders: Peyronie's disease.

General disorders and administration site conditions: Asthenia

Immune system disorders: Systemic allergic reactions including anaphylaxis, generalized and localized rash, pruritis, urticaria.

Metabolism and nutrition disorders: Hypoglycemia (in diabetic patients - see Warnings and Precautions).

Musculoskeletal and connective tissue disorders: Myalgia.

Reproductive system and breast disorders: Retroperitoneal fibrosis, sexual dysfunction, decreased libido.

Postmarketing Experience – GANFORT® (Multidose)

The following adverse reactions have been identified during postmarketing use of GANFORT™ (multidose) 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 edema, Eye swelling, Iris hyperpigmentation, Lid sulcus deepened (enophthalmos), Vision blurred, 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, Dyspnea

Skin and Subcutaneous Tissue Disorders
Alopecia, Skin hyperpigmentation (periocular), Skin discoloration (periocular)

Vascular disorders
Hypertension

OVERDOSAGE

No case of overdose has been reported, and is unlikely to occur after ocular administration.

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/m2 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 are: bradycardia, hypotension, bronchospasm, headache, dizziness, shortness of breath, and cardiac arrest. A study of patients showed that timolol did not dialyse readily.

If overdose occurs treatment should be symptomatic and supportive.

DOSAGE AND ADMINISTRATION

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. 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.

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.

HOW SUPPLIED

GANFORT® eye drops are supplied in white opaque plastic dropper bottles of 3 mL.

Store below 25°C. On prescription only. Keep out of reach of children. Keep the bottle in the outer carton.

Manufactured by:

Allergan Pharmaceuticals Ireland

Westport, Ireland

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