SCHEDULING STATUS
Schedule 3

PROPRIETARY NAME (and dosage form)
COMBIGAN eye drops (ophthalmic solution)

COMPOSITION
Each ml contains brimonidine tartrate 2,0 mg and timolol maleate equivalent to timolol 5,0 mg.
Preservative: benzalkonium chloride 0,005 % m/v

PHARMACOLOGICAL CLASSIFICATION
A. 15.4 Ophthalmic preparations. Others.

PHARMACOLOGICAL ACTION
Mechanism of action
The combination of brimonidine and timolol in an ophthalmic solution reduces intraocular pressure (IOP) by reducing aqueous humour production and increasing uveoscleral outflow.
This product contains a combination of brimonidine tartrate and timolol maleate. Each of these components is used to decrease elevated intraocular pressure.

Brimonidine tartrate is a relatively selective alpha adrenergic receptor agonist. Brimonidine tartrate lowers IOP by reducing aqueous humour production and increasing uveoscleral outflow. Timolol maleate is a non-selective beta-adrenergic receptor blocking agent that combines reversibly with the beta-adrenergic receptor. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not yet clearly established, although a fluorescein study and tonography studies indicate that its predominant action may be related to reduced aqueous humour formation.

The peak ocular hypotensive effect occurs at approximately two hours post-dosing for brimonidine tartrate and one to two hours for timolol maleate. The duration of effect is 12 hours or greater for brimonidine tartrate and 24 hours for timolol maleate.

Pharmacokinetics
Plasma brimonidine tartrate and timolol maleate concentrations were determined in healthy subjects and patients following topical dosing with the combination ophthalmic solution. Normal volunteers dosed with one drop of the combination ophthalmic solution twice daily in both eyes for seven days showed peak plasma brimonidine and timolol concentration of 0,03 ng/ml and 0,4 ng/ml, respectively. Plasma concentrations of brimonidine peaked within 1 to 4 hours after ocular dosing and declined with a systemic half-life of approximately 3 hours. Peak plasma concentrations of timolol occurred in about 1 to 3 hours post-dose. The apparent systemic half-life of timolol was about 7 hours after ocular administration.
In a crossover study with the combination ophthalmic solution in healthy volunteers, there were

no significant differences in brimonidine or timolol area-under-the-plasma-concentration-time curve between the combination ophthalmic solution and the respective monotherapy treatments. In two Phase 3 trials, brimonidine tartrate and timolol maleate plasma concentrations from the combination ophthalmic solution BID treatment group were 15 – 49 % lower than their respective monotherapy values. The lower plasma brimonidine tartrate concentration with the combination ophthalmic solution appears to be due to twice-daily dosing for the combination ophthalmic solution versus three-times dosing with brimonidine tartrate 0,2 % (ALPHAGAN).
The lower timolol maleate plasma concentrations seen with the combination ophthalmic solution, as compared to timolol maleate 0,5 %, appear to be related to a slower absorption of timolol maleate, which may be due to a difference in the benzalkonium concentrations rather than a drug-drug (brimonidine tartrate-timolol maleate) interaction.

In humans, systemic metabolism of brimonidine is extensive. It is metabolised primarily by the liver and there is no marked systemic accumulation after multiple dosing. Urinary excretion is the major route of elimination of the drug and its metabolites. Approximately 87 % of an orally-administration radioactive dose was eliminated within 120 hours, with 74 % found in the urine.

Orally administered timolol maleate is nearly completely absorbed (~90 % availability). The apparent elimination half-life of timolol maleate in plasma is 4 hours.

Timolol maleate is partially metabolised by the liver. After oral dosing, timolol maleate is subject to moderate first-pass metabolism (~50 %). Urinary excretion is the major route of elimination of timolol maleate and its metabolites. Only a small amount of unchanged medicine appears in the urine, along with its metabolites after oral dosing.

Both brimonidine and timolol are not extensively bound to plasma proteins. Brimonidine binds ~29 % and timolol is ~60 % bound to plasma proteins.

INDICATIONS
COMBIGAN ophthalmic solution is indicated for the control of intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension who are stabilised on the individual components given at the same dosages.

CONTRA-INDICATIONS
COMBIGAN (brimonidine tartrate 0,2 % and timolol maleate as timolol 0,5 %) ophthalmic solution is contra-indicated in patients with hypersensitivity to brimonidine tartrate, timolol maleate or any non-medicinal ingredient of this medication.

Safety and effectiveness in patients less than 18 years of age have not been established (see SIDE EFFECTS AND SPECIAL PRECAUTIONS).
COMBIGAN is also contra-indicated in patients with bronchial asthma or a history of bronchial

asthma; severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- or third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; or in patients receiving monoamine oxidase (MAO) inhibitor therapy.

WARNINGS

COMBIGAN is absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration of COMBIGAN ophthalmic solution. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate. (See CONTRA-INDICATIONS).

Cardiac failure

Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning therapy with COMBIGAN. In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked. At the first sign or symptom of cardiac failure, COMBIGAN should be discontinued. Caution should be exercised in treating patients with cardiovascular disease.

Diabetes mellitus

Beta-adrenergic blocking agents such as those contained in COMBIGAN should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes who are receiving insulin or oral hypoglycaemia agents). Beta-adrenergic receptor blocking agents such as those contained in COMBIGAN may mask the signs and symptoms of acute hypoglycaemia.

Angle-closure glaucoma

COMBIGAN should not be used alone in the treatment of acute angle-closure glaucoma.

Patients wearing contact lenses

The preservative in COMBIGAN, benzalkonium chloride, may be absorbed by soft (hydrophilic) contact lenses. Patients wearing soft contact lenses should be instructed to wait at least 15 minutes after instilling COMBIGAN before inserting soft contact lenses.

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 such as COMBIGAN cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication such as COMBIGAN over an extended period in patients with extensive ocular surface disease.

INTERACTIONS

Antihypertensives/Cardiac glycosides

Because of the brimonidine tartrate 0,2 % component, COMBIGAN may reduce blood pressure. Caution in the concomitant use of medicines such as antihypertensives and/or cardiac glycosides are advised.

Beta-adrenergic blockers

Patients who are receiving both an oral beta-adrenergic blocking agent and COMBIGAN should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium channel blockers or catecholamine-depleting drugs

Close observation of the patient is recommended when timolol maleate, an ingredient of COMBIGAN, is administered to patients receiving oral calcium channel blockers, catecholamine-depleting drugs such as reserpine, or beta-adrenergic blocking agents. The potential exists for additive effects and the production of hypotension, artrioventricular conduction disturbances, left ventricular failure and/or marked bradycardia.

CNS depressants

Although specific medicine interaction studies have not been conducted with COMBIGAN, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

Epinephrine

Mydriasis resulting from concomitant use of timolol maleate, an ingredient in COMBIGAN and epinephrine has been reported occasionally.

Quinidine

Potentiated systemic beta-blockade (e.g. decreased heart rate) has been reported during combined treatment with quinidine and timolol maleate, an ingredient in COMBIGAN, possibly because quinidine inhibits the metabolism of timolol maleate, via the P450 enzyme, CYP2D6.

Clonidine

Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Tricyclic antidepressants

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with COMBIGAN can

lead to resulting interference with the IOP lowering effect. No data are available on the level of circulating catecholamines after COMBIGAN is instilled. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

PREGNANCY AND LACTATION

Safety of this medicine in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

The recommended dose is one drop of COMBIGAN ophthalmic solution in the affected eye(s) twice daily (dose taken approximately 12 hours apart). If more than one topical ophthalmic product is to be used, the different products should be instilled at least 10 minutes apart.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side effects

The most commonly reported ADRs are conjunctival hyperaemia (approximately 15 % of patients) and burning sensation in the eye (approximately 11 % of patients). The majority of these cases were mild and led to discontinuation rates of only 3,4 % and 0,5 % respectively.
The following adverse reactions were reported during clinical trials with COMBIGAN:

Eye disorders

Very common (> 1/10): conjunctival hyperaemia, burning sensation.
Common (> 1/100), (< 1/10): stinging sensation in the eye, eye pruritus, allergic conjunctivitis, conjunctival folliculosis, visual disturbance, blepharitis, epiphora, corneal erosion, superficial punctuate keratitis, eye dryness, eye discharge, eye pain, eye irritation, foreign body sensation.
Uncommon (> 1/1 000), (≤ 1/100): visual acuity worsened, conjunctival oedema, follicular conjunctivitis, allergic blepharitis, conjunctivitis, vitreous floater, asthenopia, photophobia, papillary hypertrophy, eyelid pain, conjunctival blanching, corneal infiltrates, vitreous detachment.

Psychiatric disorders

Common (> 1/100), (≤ 1/10): depression

Nervous system disorders

Common (> 1/100), (≤1/10): somnolence, headache
Uncommon (> 1/1 000), (≤ 1/100): dizziness, syncope

Cardiac disorders

Uncommon (> 1/1 000), (≤ 1/100): congestive heart failure, palpitations

Vascular disorders
Common (> 1/100), (≤ 1/10): hypertension

Respiratory, thoracic and mediastinal disorders
Uncommon (> 1/1 000), (≤ 1/100): rhinitis, nasal dryness

Gastrointestinal disorders
Common (> 1/100), (≤ 1/10): oral dryness
Uncommon (> 1/1 000), (≤ 1/100): taste perversion

Skin and subcutaneous tissue disorders
Common (> 1/100), (≤ 1/10): eyelid oedema, eyelid pruritus, eyelid erythema
Uncommon (> 1/1 000), (≤ 1/100): allergic contact dermatitis

General disorders and administration site conditions
Common (> 1/100), (≤ 1/10): asthenic conditions

Investigations
Common (> 1/100), (≤ 1/10): LFTs abnormal

Additional adverse events (frequency unknown) that have been seen with one of the components and may potentially occur also with COMBIGAN:

Brimonidine
Eye disorders: iritis, miosis
Psychiatric disorders: insomnia
Cardiac disorders: arrhythmias (including bradycardia and tachycardia)
Vascular disorders: hypotension
Respiratory, thoracic and mediastinal disorders: upper respiratory symptoms, dyspnoea
Gastrointestinal disorders: gastrointestinal symptoms
*General disorders and administration site condition*s: systemic allergic reactions

Timolol
Eye disorders: decreased corneal sensitivity, diplopia, ptosis, choroidal detachment (following filtration surgery), refractive changes (due to withdrawal of miotic therapy in some cases)
Psychiatric disorders: insomnia, nightmares, decreased libido
Nervous system disorders: memory loss, increase in signs and symptoms of myasthenia gravis, paresthaesia, cerebral ischaemia
Ear and labyrinth disorders: tinnitus
Cardiac disorders: heart block, cardiac arrest, arrhythmia, bradycardia
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) dyspnoea, cough, respiratory failure
Gastrointestinal disorders: nausea, diarrhoea, dyspepsia
Skin and subcutaneous tissue disorders: alopecia, psoriasiform rash or exacerbation of psoriasis
Musculoskeletal, connective tissue and bone disorders: systemic lupus erythematosus
Renal and urinary disorders: Peyronie's disease
General disorders and administration site conditions: oedema, chest pain

Causal relationship unknown: The following adverse reactions have been reported with timolol maleate an ingredient of COMBIGAN: aphakic cystoid macular oedema, nasal congestion, anorexia, CNS effects (e.g. behavioural changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances), hypertension, retroperitoneal fibrosis and pseudopemphigoid, but a causal relationship could not be established.

Clinical laboratory test: Clinically important changes in standard laboratory parameters were rarely associated with the administration of systemic timolol maleate. Slight increases in blood urea, serum potassium and serum uric acid and triglycerides, and slight decreases in haemoglobin and haematocrit and HDL-cholesterol occurred, but were not progressive or associated with clinical manifestations.

Timolol maleate (systemic formulation): Adverse reactions reported in clinical experience with oral timolol maleate may be considered potential side-effects of ophthalmic timolol maleate. For other detailed information, please consult the package insert for timolol maleate.

Serious reports of side-effects in paediatric patients: Several serious side-effects have been reported in association with the administration of brimonidine tartrate ophthalmic solution 0,2 % to infants in the age of 28 days to 3 months. These reactions included: bradycardia, hypotension, hypothermia, hypotonia, apnoea, dyspnoea, hypoventilation, cyanosis and lethargy resulting in hospitalisation. COMBIGAN should not be used in patients younger than 18 years of age.

Precautions
General: Patients prescribed IOP-lowering medication should be routinely monitored for IOP. COMBIGAN ophthalmic solution should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension or thromboangitis obliterans.
Hypersensitivity: Because of the brimonidine tartrate component COMBIGAN should be used with caution in patients with known hypersensitivity to other alpha-adrenoceptor agonists. While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic

reaction to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. These patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions since timolol maleate may blunt the beta-agonist effect of epinephrine. In such cases, alternatives to epinephrine should be considered.

Contact lenses: **COMBIGAN contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses; therefore, COMBIGAN should not be administered while wearing these lenses. The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.**

Choroidal detachment: Choroidal detachment after filtration procedures has been reported with administration of aqueous suppressant therapy (e.g. timolol maleate, acetazolamide). Management of eyes with chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously.

Major surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking medication including COMBIGAN prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

Thyrotoxicosis: Beta-adrenergic blocking agents as contained in COMBIGAN may mask certain clinical signs of hyperthyroidism (e.g. tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

Muscle weakness: Beta-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalised weakness). Timolol maleate, as contained in COMBIGAN, has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Cerebrovascular insufficiency: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, COMBIGAN should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with COMBIGAN, alternative therapy should be considered.

Liver/renal Impairment: COMBIGAN has not been studied in patients with hepatic or renal impairment; caution should be exercised in treating such patients.
Obstructive pulmonary disease: Patients with chronic obstructive pulmonary disease (e.g. chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma

in which COMBIGAN is contra-indicated) should in general not receive beta-blocking agents, including COMBIGAN.

Use in paediatrics: The use of COMBIGAN in paediatric patients is not recommended. Several serious adverse reactions have been reported in association with the administration of brimonidine tartrate ophthalmic solution 0,2 % to infants in the age range of 28 days to 3 months. COMBIGAN should not be used in patients younger than 18 years of age.

Driving or using machines: COMBIGAN can potentially cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

Information for patients: Patients should be instructed to avoid allowing the tip of the dispensing container to make contact with the eye or surrounding structures. If handled improperly, ocular solutions can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption to the ocular epithelial surface.

Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g. trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

If more than one topical ophthalmic medicine is being utilised, the medicines should be administered at least ten minutes apart.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

No data are available on overdosage with COMBIGAN ophthalmic solution in humans. There have been reports of inadvertent overdosage with timolol maleate ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest.

Treatment of an oral overdosage includes supportive and symptomatic therapy; a patent airway should be maintained. Evacuation of the stomach should be considered during the first few hours of overdosage.

A study of patients with renal failure showed that timolol maleate did not dialyse readily.

Specific therapeutic measures for the treatment of overdosage with timolol maleate are reproduced below for ease of reference:

Gastric lavage: If ingested.
Symptomatic bradycardia: Use of atropine sulphate intravenously in a dosage of 0,25 to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.
Hypotension: Use sympathomimetic pressor medication therapy, such as dopamine, dobutamine or levarterenol. In refractory cases the use of glucagon hydrochloride has been reported to be useful.
Bronchospasm: Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.
Acute cardiac failure: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophyline is suggested. This may be followed if necessary by glucagon which has been reported to be useful.
Heart block (second or third degree): Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

IDENTIFICATION
COMBIGAN ophthalmic solution is a clear, greenish-yellow to light greenish-yellow solution, essentially free from particulate matter.

PRESENTATION
COMBIGAN is supplied sterile in white, opaque LDPE bottles with tips and high impact polystyrene (HIPS) caps, containing 5 ml solution.

STORAGE INSTRUCTIONS
COMBIGAN should be stored below 25 ºC, protected from light. Do not refrigerate. To avoid contamination of the solution keep container tightly closed. Do not touch dropper tip to any surface. Discard contents 30 days after opening the bottle. Contents are sterile if seal is intact. KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER
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