SCHEDULING STATUS
Schedule 3

PROPRIETARY NAME AND DOSAGE FORM
BETAGAN 0,5 % Liquifilm (Sterile Ophthalmic Solution)

COMPOSITION
BETAGAN 0,5 % Liquifilm Sterile Ophthalmic solution contains:
Levobunolol hydrochloride 5 mg/ml
Excipients:
Polyvinyl alcohol, sodium chloride, disodium edetate, sodium phosphate dibasic heptahydrate, potassium dihydrogen phosphate, purified water, sodium metabisulphite (E223).

Benzalkonium chloride 0,004 % m/v.

PHARMACOLOGICAL CLASSIFICATION
A 15.4. Ophthalmic preparations. Others

PHARMACOLOGICAL ACTION
Pharmacodynamic properties
Levobunolol is a non-cardioselective beta-adrenoreceptor blocking agent, equipotent at both beta1, and beta2 receptors. Levobunolol is 60 times more potent than its dextro isomer in its beta-blocking activity. In order to obtain the highest degree of beta-blocking potential without increasing the potential for direct myocardial depression, the levo isomer, levobunolol, is used. Levobunolol does not have significant local anaesthetic (membrane stabilising) or intrinsic sympathomimetic activity.

Levobunolol, when instilled in the eye, will lower elevated intraocular pressure as well as normal intraocular pressure, whether or not accompanied by glaucoma.

The primary mechanism of action of levobunolol in reducing intraocular pressure is most likely a decrease in aqueous humour production. Levobunolol reduces intraocular pressure with little or no effect on pupil size.

Pharmacokinetic properties
The onset of action with one drop of levobunolol can be detected within one hour after instillation, with maximum effect seen between two and six hours. A significant decrease can be maintained for up to 24 hours following a single dose.

INDICATIONS

BETAGAN 0,5 % is indicated for the control of intraocular pressure in chronic open angle glaucoma and ocular hypertension.

CONTRA INDICATIONS

Hypersensitivity to the active ingredient 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 and third-degree atrioventricular block not controlled with a pace maker, overt cardiac failure or cardiogenic shock.

WARNINGS AND SPECIAL PRECAUTIONS

In the perioperative period it is generally unwise to reduce the dosage of BETAGAN 0,5 %. A patient's normal tachycardiac response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard.

BETAGAN 0,5 % contains benzalkonium chloride as a preservative.

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.

BETAGAN 0,5 % may be absorbed systemically so the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-blockers may occur.

Caution should be exercised in treating patients with severe or unstable and uncontrolled cardiovascular disease including first degree atrioventricular block. Cardiac failure should be adequately controlled before beginning 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 failure have been reported following administration of levobunolol as contained in BETAGAN 0,5 %.

Patients with mild/moderate chronic obstructive pulmonary disease should, in general, not receive beta blockers, including BETAGAN 0,5 %; however, if BETAGAN 0,5 % is deemed necessary in such patients, it should be administered with caution.

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be exaggerated when BETAGAN 0,5 % is given to patients already receiving a systemic beta blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended.

In patients with angle closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. BETAGAN 0,5 % has little or no effect on the pupil. When BETAGAN 0,5 % is used to reduce elevated intra-ocular pressure in angle-closure glaucoma it should be used with a miotic and not alone.

In patients with severe renal impairment on dialysis, treatment with levobunolol has been associated with pronounced hypotension (See Dosage and Directions for use).

Levobunolol 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 BETAGAN 0,5 %.

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

BETAGAN 0,5 % must be used with caution in patients with metabolic acidosis and untreated phaeochromocytoma.

BETAGAN 0,5 % should be administered with caution in patients subject to spontaneous hypoglycaemia or to uncontrolled diabetic patients (especially those with labile diabetes) as beta-blockers may mask the signs and symptoms of acute hypoglycaemia. The indicatory signs of acute hypoglycaemia may be masked, in particular tachycardia, palpitations and sweating.

BETAGAN 0,5 % should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

While using BETAGAN 0,5 %, 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.

If discontinuation of treatment with BETAGAN 0,5 % is needed in patients with coronary heart disease, therapy should be withdrawn gradually to avoid rhythm disorders, myocardial infarction or sudden death.

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

BETAGAN 0,5 % may induce dryness of eyes. Patients with corneal diseases should be treated with caution. In patients with chronic eye inflammation and corneal dystrophy BETAGAN 0,5 % should only be applied in the event of stringent diagnosis & under continuous monitoring at short intervals.

Skin rashes and/or dry eyes associated with the use of beta-blockers have been reported. The incidence is small and symptoms have stopped on withdrawal of the beta-blockers. Discontinuation of the use of BETAGAN 0,5 % should be considered if these symptoms are reported but cessation of treatment should be gradual.

The preservative in BETAGAN 0,5 %, benzalkonium chloride, may cause eye irritation. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Avoid contact with soft contact lenses.

BETAGAN 0,5 % contains sodium metabisulphite which may cause severe hypersensitivity reactions and bronchospasm.

Athletes should be aware that BETAGAN 0,5 % contains levobunolol that may induce a positive result in anti-doping controls.

Paediatric population
Safety and effectiveness in children have not been established.

Effects on the ability to drive and use machines
BETAGAN 0,5 % may cause transient blurring of vision, fatigue and/or drowsiness which may impair the ability to drive or operate machines. The patient should wait until these symptoms have cleared before driving or using machinery.

INTERACTIONS
No interaction studies have been performed.

Although specific medicine interactions studies have not been conducted with BETAGAN 0,5 %, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

There is potential for additive effects resulting in hypotension, and/or marked bradycardia when BETAGAN 0,5 % is administered concomitantly with anti-hypertensive medicines (oral calcium channel blockers, rauwolfia alkaloids, guanethidine, beta-blocking agents), anti-dysrhythmic medicines, digitalis glycosides (digoxin) or parasympathomimetics.

Caution should be exercised and patients must be monitored when BETAGAN 0,5 % is used concomitantly with oral beta-adrenergic blocking agents, because of the potential for additive effects on systemic beta blockade.

Enhanced hypotensive effect is seen when baclofen is given with beta-blockers. Since some systemic absorption may follow topical application of BETAGAN 0,5 %, regular blood pressure monitoring is advised.

Although levobunolol has little effect on the size of the pupil, mydriasis has been reported when BETAGAN 0,5 % has been used with mydriatic agents such as epinephrine (adrenaline).

Beta-blockers such as levobunolol may increase the hypoglycaemic effect of antidiabetic agents. BETAGAN 0,5 % 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 using BETAGAN 0,5 %.

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

Concomitant use of BETAGAN 0,5 % with anaesthetic medicines may attenuate compensatory tachycardia and increase the risk of hypotension (see "Warnings and special precautions"), and therefore the anaesthetist must be informed if the patient is using BETAGAN 0,5 %.

Caution must be exercised if BETAGAN 0,5 % is used concomitantly with iodine contrast products or intravenously administered lidocaine.
Cimetidine may increase the plasma concentrations of levobunolol.

No data on the level of circulating catecholamines after BETAGAN 0,5 % administration are available. Caution, however, is advised in patients taking medication which can affect the metabolism and uptake of circulating amines e.g. phenothiazines, methylphenidate, reserpine because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope or postural hypotension.

Although specific medicine interactions studies have not been conducted with BETAGAN 0,5 %, known additive intraocular pressure (IOP) lowering effect with prostamides, prostaglandins, alpha-agonists, carbonic anhydrase inhibitors and pilocarpine should be considered.

Digitalisation of patients receiving long-term beta-blocker therapy may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of negative chronotropic effect of the two medicines. Careful control of dosages and of the individual patient response (and notably pulse rate) is essential in this situation.

PREGNANCY AND LACTATION

Pregnancy

Safety and/or efficacy during pregnancy have not been established.

Epidemiological studies show 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.

Lactation

Levobunolol is excreted in breast milk.
BETAGAN 0,5 % should not be used by women breastfeeding their infants.

DOSAGE AND DIRECTIONS FOR USE

Adults (including the elderly): the recommended dosage is one drop of BETAGAN 0,5 % in the affected eye(s) twice a day.

BETAGAN 0,5 % has not been studied in patients with hepatic or renal impairment. Therefore, caution should be used in treating such patients (see “Warnings and special precautions”).

BETAGAN 0,5 % is not recommended for use in children due to lack of safety and efficacy data (see “Paediatric population” under “Warnings and Special Precautions”).

Method of administration: topical into the conjunctival sac.
If required, BETAGAN 0,5 % may be used with other agents to lower intra-ocular pressure. The use of two topical beta-adrenergic blocking agents is not recommended (see “Interactions”).

Intraocular pressure should be measured approximately four weeks after starting treatment with BETAGAN 0,5 % as a return to normal ocular pressure can take a few weeks.

To reduce possible systemic absorption, it is recommended that the lachrymal sac is compressed at the medial canthus (punctual occlusion) for one minute. This should be performed immediately following the instillation of each drop.

Transfer from other beta-blocking treatment
When another beta blocking agent is being used treatment must be discontinued after a full day of therapy. Start treatment with BETAGAN 0,5 % the next day with one drop of BETAGAN 0,5 % topically applied into the conjunctival sac in the affected eye(s) once or twice a day.

If BETAGAN 0,5 % is to replace a combination of anti-glaucoma products, only a single product should be removed at a time.

SIDE EFFECTS
Within each frequency grouping, side effects are presented in order of decreasing seriousness. The following terminologies have been used in order to classify the occurrence of side effects: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1 000 to <1/100); Rare (≥1/10 000 to <1/1 000); Very rare (<1/10 000), not known (cannot be estimated from the available data).

Immune system disorders
Not known: Hypersensitivity reaction including symptoms or signs of eye allergy and skin allergy

Psychiatric disorders
Not known: Depression

Nervous system disorders
Not known: Ataxia, confusion, dizziness, somnolence, lethargy, headache, insomnia

Eye disorders
Very common: Eye irritation, conjunctival irritation, eye pain
Common: Blepharitis, conjunctivitis
Not known: Conjunctival/ocular hyperaemia, conjunctivitis allergic, decreased corneal reflex, iridocyclitis, keratitis, punctate keratitis, visual disturbance, eye/eyelids pruritus, eye/eyelid oedema, eye discharge, increased lacrimation, dry eyes, blurred vision, foreign body sensation in the eye

Cardiac disorders
Not known: Syncope, bradycardia, atrioventricular block, palpitations

Vascular disorders
Not known: Hypotension, Raynaud's phenomenon

Respiratory, thoracic, and mediastinal disorders
Not known: Asthma, dyspnoea, throat irritation, nasal discomfort

Gastrointestinal disorders
Not known: Nausea

Skin and subcutaneous tissue disorders
Not known: Alopecia, urticaria, dermatitis contact (including allergic contact dermatitis), rash, erythema of the eyelid, eyelid eczema, skin exfoliation, lichenoid keratosis, pruritus

General disorders and administration site conditions
Not known: Face oedema, fatigue

Additional adverse reactions have been seen with other ophthalmic beta-blockers and may potentially occur with BETAGAN 0.5 %:

Eye disorders: Choroidal detachment following filtration surgery, corneal erosion, diplopia, ptosis
Immune system disorders: Anaphylaxis, systemic allergic reactions including angioedema
Metabolism and nutrition disorders: Hypoglycaemia
Psychiatric disorders: Insomnia, memory loss, nervousness, nightmares
Nervous system disorders: Cerebral ischemia, cerebrovascular accident, increases in signs and symptoms of myasthenia gravis, paresthaesia
Cardiac disorders: Arrhythmia, cardiac arrest, cardiac failure, chest pain, congestive heart failure, oedema
Vascular disorders: Cold hands and feet
Respiratory, thoracic and mediastinal disorders: Bronchospasm, cough, respiratory failure (predominantly in patients with pre-existing bronchospastic disease), shortness of breath
Gastrointestinal disorders: Upper abdominal pain, diarrhoea, dysguesia, dry mouth, dyspepsia, vomiting
Skin and subcutaneous tissue disorders: Psoriasiform rash or exacerbation of psoriasis
Musculoskeletal and connective tissue disorders: Arthropathy, myalgia
Reproductive system and breast disorders: Decreased libido, sexual dysfunction
General disorders and administration site conditions: Thirst

The following events have been reported with systemic beta-blocker formulations and may occur with the topical use of BETAGAN 0,5 %:

Nervous system disorders: Sleep disturbance
Psychiatric disorders: Impotence, hallucinations, nightmares
Cardiac disorders: Cardiac failure, marked bradycardia
Vascular disorders: Cold extremities, Raynaud's phenomenon, worsening intermittent claudication
Gastrointestinal disorders: Abdominal pain upper, vomiting, diarrhoea
Respiratory, thoracic, and mediastinal disorders: Bronchospasm
Endocrine disorders: Hypoglycaemia
Skin and subcutaneous tissue disorders: Angioedema (Quincke's oedema), cutaneous and psoriasis-like symptoms

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

There are no data available on human overdosage with BETAGAN 0,5 %. Should accidental ocular overdosage occur, flush eye(s) with water or normal saline. If accidentally ingested, systemic symptoms may result and efforts to decrease further absorption may be appropriate.

The symptoms associated with systemic overdosage are most likely to be bradycardia, hypotension, bronchospasm and cardiac failure. Therapy for overdosage of a beta-adrenergic blocking agent should be instituted, such as intravenous administration of atropine sulphate 0,25 mg to 2 mg to induce vagal blockade.

Conventional therapy for hypotension, bronchospasm, heart block and cardiac failure may be necessary.

IDENTIFICATION

BETAGAN 0,5 % Liquifilm is a colourless to light yellow solution.

PRESENTATION

BETAGAN 0,5 % Liquifilm is supplied in sterile dropper bottles containing 5 ml solution.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Protect from light. Do not use more than 30 days after opening. KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

S/15.4/0194

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

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