DATA SHEET

1. PRODUCT NAME
BETAGAN® 5mg/mL eye drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
levobunolol hydrochloride 5mg/mL

For full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM
Clear, colourless to slightly yellow, sterile ophthalmic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Control of intraocular pressure in patients with open angle glaucoma.
Control of ocular hypertension.
Treatment of acute increased intraocular pressure following laser capsulotomy and extra-capsular cataract extraction.

4.2 Dosage and Method of Administration
The recommended dose is one drop of BETAGAN® 0.5% eye drops in the affected eye(s) twice a day. Studies have also shown that IOP is controlled in many patients with one drop of BETAGAN® 0.5% eye drops in the affected eye(s) once a day. Careful monitoring of patients is advised, particularly in the first few days after starting treatment or if the dose of BETAGAN® eye drops is increased.

Dosages above one drop of BETAGAN® 0.5% eye drops twice daily are not generally more effective. If the patient's IOP is not at a satisfactory level on this regimen, concomitant therapy with dipivefrine and/or adrenaline, and/or pilocarpine and other miotics, and/or systemically administered carbonic anhydrase inhibitors, such as acetozolamide, can be instituted.

In order to minimise systemic absorption of BETAGAN® eye drops, apply pressure to the tear duct immediately following administration of the drug.

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

4.3 Contraindications
BETAGAN® eye drops are contraindicated in those individuals with bronchial asthma or with a history of bronchial asthma or severe chronic obstructive pulmonary disease (see 4.4 Special Warnings and Precautions for use); sinus bradycardia; sick sinus syndrome (including sino-atrial nodal block); second or third degree atrioventricular block not controlled with a pacemaker; overt cardiac failure (see 4.4 Special Warnings and Precautions for use); cardiogenic shock; or hypersensitivity to any component of this product (see 5.3 Preclinical Safety Data).

4.4 Special Warnings and Precautions for use

BETAGAN® eye drops should be used with caution in patients with known hypersensitivity to other ß-adrenergic blocking agents. Use with caution in patients with known diminished pulmonary function.

In patients with angle-closure glaucoma, the immediate objective of treatment is to re-open the angle. This requires, in most cases, constricting the pupil with a miotic. BETAGAN® eye drops have little or no effect on the pupil. When BETAGAN® eye drops are used to reduce elevated IOP in angle-closure glaucoma, it should be followed by a miotic and not used alone.

As with other topically applied ophthalmic drugs, BETAGAN® eye drops may be absorbed systemically. The same adverse reactions found with systemic administration of ß-adrenergic blocking agents may occur with topical administration. 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 with topical application of ß-adrenergic blocking agents (see 4.3 Contraindications).

The preservative in BETAGAN®, benzalkonium chloride, may be absorbed by soft contact lenses. BETAGAN® eye drops should not be used while wearing soft contact lenses. Patients should be instructed to remove lenses before instilling BETAGAN® eye drops and wait at least 15 minutes after instilling BETAGAN® eye drops before re-inserting their lenses.

Cardiac Failure*:* Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by ß-adrenergic receptor blockade may precipitate more severe failure.

BETAGAN® should be used with caution in patients with cardiovascular disease (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension.

Due to its negative effects on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

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

Obstructive Pulmonary Disease: Patients with mild/moderate chronic obstructive pulmonary disease should, in general, not receive beta blockers, including levobunolol; however, if levobunolol is deemed necessary in such patients, it should be administered with caution.

In Patients without a History of Cardiac Failure*:* Continued depression of the myocardium with ß-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign of symptoms of cardiac failure, BETAGAN® eye drops should be discontinued.

Non-allergic Bronchospasm*:* In patients with non-allergic bronchospasm or with a history of non-allergic bronchospasm, (e.g. chronic bronchitis, emphysema), BETAGAN® eye drops should be administered with caution since they may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $ß_2$-receptors.

Major Surgery*:* The necessity or desirability of withdrawal of ß-adrenergic blocking agents prior to major surgery is controversial. ß-adrenergic blockade impairs the ability of the heart to respond to ß-adrenergically mediated reflex stimuli. Levobunolol may impair compensatory tachycardia and may augment the risk of hypotension when used with general anaesthesia in surgical procedures. Some patients receiving ß-adrenergic blocking agents have been subject to protracted severe hypotension during anaesthesia. For these reasons, in patients undergoing elective surgery, gradual withdrawal of ß-adrenergic blocking agents may be appropriate. The anaesthetist must be informed if the patient is using levobunolol.

If necessary during surgery, the effects of ß-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoprenaline, dopamine, dobutamine or noradrenaline acid tartrate (see 4.9 Overdose).

Diabetes Mellitus*:* ß-adrenergic blocking agents should be administered with caution to patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycaemic agents. ß-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycaemia.

Hyperthyroidism/Thyrotoxicosis*:* ß-adrenergic blocking agents may mask certain clinical signs (e.g. tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of ß-adrenergic blocking agents which might precipitate a thyroid storm.

Metabisulfite Sensitivity*:* Contains sodium metabisulfite, a sulfite which may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic rather than in non-asthmatic people.

Muscle Weakness*:* ß-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalised weakness).

Risk of anaphylactic reaction: While taking ß blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of adrenaline used to treat allergic reactions.

Corneal diseases: 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-andrenergic blocking agents because of the potential for additive effects on systemic beta-blockage. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended.

4.5 Interaction with other medicines and other forms of interactions

BETAGAN® eye drops should be used with caution in patients who are receiving a ß-adrenergic receptor blocking agent orally, because of the potential for additive effects on systemic ß-blockade and on intraocular pressure.

Although BETAGAN® eye drops used alone have little or no effect on pupil size, mydriasis resulting from concomitant use of BETAGAN® eye drops and mydriatic agents such as adrenaline may occur.

Close observation of the patient is recommended when a ß-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope or postural hypotension.

There is potential for additive effects resulting in hypotension, and/or marked bradycardia when eye drops with levobunolol are administered concomitantly with oral calcium channel blockers, beta-blocking agents, anti-arrhythmics (including amiodarone) digitalis glycosides or parasympathomimetics.

Patients receiving ß-adrenergic blocking agents along with either oral or intravenous calcium antagonists should be monitored for possible atrioventricular conduction disturbances, left ventricular failure and hypotension. In patients with impaired cardiac function, simultaneous use should be avoided altogether.

The concomitant use of ß-adrenergic blocking agents with digitalis may have additive effects on prolonging atrioventricular conduction time. Phenothiazine-related compounds and ß-adrenergic blocking agents may have additive hypotensive effects due to the inhibition of each other's metabolism.

Beta blockers may increase the hypoglycaemic effect of antidiabetic agents. Beta blockers can mask the signs and symptoms of hypoglycaemia.

Concomitant use of a beta blocker with anaesthetic drugs may attenuate compensatory tachycardia and increase the risk of hypotension. The anaesthetist must therefore be informed if the patient is taking levobunolol.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Pregnancy Category C.

Beta adrenergic blocking agents may cause pharmacological effects of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) in the fetus and newborn infant. During the latter stages of pregnancy and birth, these drugs should be given only after weighing the needs of the mother against the risk to the fetus. If BETAGAN® is administered until delivery, the neonate should be carefully monitored during the first days of life.

There are no adequate and well-controlled studies in pregnant women. BETAGAN® eye drops should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is not known whether the drug is excreted in human milk. Systemic ß-blockers and topical timolol maleate are known to be excreted in human milk. Caution should be exercised when BETAGAN® eye drops are administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a lifetime study of mice there were statistically significant ($p \leq 0.05$) increases in the incidence of benign leiomyomas in female mice at 200 mg/kg/day (14,000 times the maximum recommended human dose for glaucoma), but not at 12 or 50 mg/kg/day (850 and 3,500 times the human dose). In a two-year oral study of levobunolol HCl in rats there was a statistically significant ($p \leq 0.05$) increase in the incidence of hepatomas in male rats administered 12,800 times the recommended human dose for glaucoma. Similar differences were not observed in rats administered oral doses equivalent to 350 times to 2,000 times the recommended human dose for glaucoma.

Levobunolol did not show evidence of mutagenic activity in a battery of microbiological and mammalian *in vitro* and *in vivo* assays. Reproduction and fertility studies in rats showed no adverse effects on male or female fertility at doses up to 1,800 times the recommended human dose for glaucoma.

4.7 Effects on Ability to Drive and Use Machines
As BETAGAN® eye drops may cause transient blurring, fatigue and/or drowsiness on instillation, caution is required with the use of hazardous machinery or driving, which are not recommended unless symptoms have cleared.

4.8 Undesirable Effects
The following adverse effects have been reported rarely with the use of BETAGAN® eye drops: iridocyclitis, headache, transient ataxia, dizziness, lethargy, urticaria and pruritus.

Decreased corneal sensitivity has been noted in a small number of patients. Although levobunolol has minimal membrane-stabilising activity, there remains the possibility of decreased corneal sensitivity after prolonged use.

Clinical Studies Experience
Frequency categories: 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 available data).

Eye Disorders
Very Common: Eye irritation, Eye pain
Common: Blepharitis, Conjunctivitis

Postmarketing Experience: Levobunolol hydrochloride

The following adverse reactions have been identified during postmarketing use of levobunolol eye drops in clinical practice. Because postmarketing reporting of these reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions.

Eye Disorders
Conjunctival/Ocular hyperemia, Conjunctivitis allergic, Corneal reflex decreased, Eye discharge, Eye/Eyelid edema, Eye/Eyelids pruritus, Foreign body sensation in the eye, Iridocyclitis, Keratitis, Lacrimation increased, Punctate keratitis, Vision blurred

General Disorders and Administration Site Conditions
Face edema, Fatigue/Asthenia

Nervous System Disorders
Confusion, Dizziness, Headache, Insomnia, Lethargy, Somnolence

Psychiatric Disorders
Depression

Cardiac Disorders
Atrioventricular block, Bradycardia, Palpitations, Syncope

Vascular Disorders
Hypotension, Raynaud's phenomenon

Respiratory, Thoracic, and Mediastinal Disorders
Asthma, Dyspnea, Nasal discomfort, Throat irritation

Gastrointestinal Disorders
Nausea

Skin and Subcutaneous Tissue Disorders
Alopecia, Dermatitis contact (including allergic contact dermatitis), Erythema of eyelid, Eyelid eczema, Lichenoid keratosis, Pruritis, Rash, Skin exfoliation, Urticaria

Adverse Drug Reactions – Other Ophthalmic Beta-blockers
The following additional adverse reactions have been reported with ophthalmic use of $ß_1$ and $ß_2$ (non-selective) adrenergic blocking agents:

Eye Disorders
Choroidal detachment following filtration surgery (see 4.4 Special Warnings and Precautions for use), Corneal erosion, Diplopia, Dry eye, Ptosis, Visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases)

Immune System Disorders
Anaphylaxis, Systemic allergic reactions including angioedema

Metabolism and Nutrition Disorders
Hypoglycaemia, Masked symptoms of hypoglycaemia in insulin-dependent diabetics (see 4.4 Special Warnings and Precautions for use)

Psychiatric Disorders
Insomnia, Memory loss, Nervousness, Nightmares

Nervous System Disorders
Cerebral ischemia, Cerebrovascular accident, Increases in signs and symptoms of myasthenia gravis, Paresthesia.

Cardiac Disorders
Arrhythmia, Heart block, Cerebral vascular accident. Cerebral ischemia, Cardiac arrest, Cardiac failure, Chest pain, Congestive heart failure, Edema.

Vascular Disorders
Cold hands and feet

Respiratory, Thoracic, and Mediastinal Disorders
Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), Cough, Respiratory failure (predominantly in patients with pre-existing bronchospastic disease), Shortness of breath

Gastrointestinal Disorders
Abdominal pain upper, Diarrhea, Dysgeusia, Dry mouth, Dyspepsia, Vomiting.

Skin and Subcutaneous Tissue Disorders
Psoriasiform rash or exacerbation of psoriasis, Hypersensitivity including localised and generalised rash.

Musculoskeletal and Connective Tissue Disorders
Arthropathy, Myalgia

Reproductive System and Breast Disorders
Decreased libido, Sexual dysfunction

General Disorders and Administration Site Conditions
Thirst

Other reactions associated with the oral use of non-selective adrenergic blocking agents should be considered potential effects with ophthalmic use of these agents.

4.9 Overdose
No data are available regarding overdose in humans. Should accidental ocular overdose occur, flush eye(s) with water or normal saline. If accidentally ingested, efforts to decrease further absorption may be appropriate (gastric lavage).

The most common signs and symptoms to be expected with overdose of a systemic ß-adrenergic blocking agent are symptomatic bradycardia, hypotension, bronchospasm and acute cardiac failure. Should these symptoms occur, discontinue BETAGAN® eye drops and initiate appropriate supportive therapy. The following supportive measures should be considered:

1. **Symptomatic bradycardia**: Use atropine sulfate intravenously in a dosage of 0.25 mg to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoprenaline hydrochloride should be administered cautiously. In refractory cases the use of transvenous cardiac pacemaker should be considered.

2. **Hypotension**: Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or noradrenaline acid tartrate. In refractory cases the use of glucagon hydrochloride may be useful.

3. **Bronchospasm**: Use isoprenaline hydrochloride. Additional therapy with aminophylline may be considered.

4. **Acute cardiac failure**: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed, if necessary, by glucagon hydrochloride which may be useful.

5. **Heart block (second or third degree)**: Use isoprenaline hydrochloride or a transvenous pacemaker.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACEUTICAL PROPERTIES

5.1. Pharmacodynamic Properties

Levobunolol hydrochloride (HCl) is a non-cardioselective ß-adrenoceptor blocking agent, equipotent at both ß1 and ß2 receptors. Levobunolol HCl is greater than 60 times more potent than its dextro isomer in its ß-blocking activity, yet equipotent in its potential for direct myocardial depression. Accordingly, the levo isomer, levobunolol HCl, is used. Levobunolol HCl does not have significant local anaesthetic (membrane stabilising) or intrinsic sympathomimetic activity.

The primary mechanism of the ocular hypotensive action of levobunolol hydrochloride (HCl) in reducing IOP appears to be a decrease in aqueous humor production. BETAGAN® eye drops reduce IOP with little or no effect on pupil size or accommodation in contrast to the miosis which cholinergic agents are known to produce. The blurred vision and night blindness often associated with miotics would not be expected and have not been reported with the use of BETAGAN® eye drops. This is particularly important in cataract patients with central lens opacities who would experience decreased visual acuity with pupillary constriction.

ß-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, ß-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

ß-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

BETAGAN® eye drops (levobunolol HCl) have been shown to be an active agent in lowering elevated as well as normal intraocular pressure (IOP), whether or not accompanied by glaucoma. Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

The onset of action with one drop of BETAGAN® eye drops can be detected within one hour after treatment, with maximum effect seen between 2 and 6 hours. A significant decrease in IOP can be maintained for up to 24 hours following a single dose.

5.2. Pharmacokinetic Properties
Nil

5.3. Preclinical Safety Data
In several controlled clinical studies of four years duration, IOP was well-controlled in the majority of subjects treated with 0.5% levobunolol HCl b.i.d, with annual retention rates of over 80%. The mean IOP decrease from baseline was between 5.8 mmHg and 7.8 mmHg. A total of 72 subjects remained on this agent over the entire four years treatment. No significant effects on pupil size, tear production or corneal sensitivity was observed in any of these studies. BETAGAN® eye drops at the concentrations tested, when applied topically, decreased heart rate and blood pressure in some patients. Efficacy was at least comparable to that of timolol over the entire study period.

In clinical trials the use of BETAGAN® eye drops has been associated with transient ocular burning and stinging in about 1 in 3 patients, and blepharoconjunctivitis in about 1 in 20 patients. Decreases in heart rate and blood pressure have been reported (see 4.3 Contraindications and 4.4 Special Warnings and Precautions for use).

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients
PRESERVATIVE: benzalkonium chloride

INACTIVES: polyvinyl alcohol (LIQUIFILM®), sodium metabisulfite, disodium edetate, sodium phosphate dibasic, potassium phosphate, sodium chloride, purified water and hydrochloric acid or sodium hydroxide to adjust pH.

6.2. Incompatibilities
In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3. Shelf Life:
24 months

6.4. Special Precautions for Storage:
Store below 25°C.

Protect from light and excessive heat.

Discard unused contents 4 weeks after opening.

To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Contents are sterile if seal is intact.

6.5. Nature and Contents of Container
5 mL dropper bottles

6.6. Special Precautions for Disposal
No special requirements for disposal

7. MEDICINE SCHEDULE
Prescription Medicine

8. SPONSOR
Allergan New Zealand Ltd
Corner of Manu Tapu Drive and
Joseph Hammond Place
Auckland International Airport
Mangere AUCKLAND

Toll free telephone: 0800 659 912

9. DATE OF FIRST APPROVAL
15 December 1985

10. DATE OF REVISION OF TEXT
29 March 2017

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SUMMARY TABLE OF CHANGES

Sections changed	Summary of new information
All headings amended to align to Medsafe's updated DS requirements and sections within the Data Sheet have been moved under the appropriate headings in line with Medsafe's updated DS requirements.	
1	Amended in line with Medsafe's updated DS requirements
2	Amended in line with Medsafe's updated DS requirements
4.3	Addition of safety information in line with the Company Core Data Sheet
4.8	Addition of safety information in line with the Company Core Data Sheet
4.9	Additional information included in line with Medsafe's updated DS requirements
6.2	Additional information included in line with Medsafe's updated DS requirements
6.6	Additional information included in line with Medsafe's updated DS requirements
9.	Date of first approval of BETAGAN® 0.5 mg/mL has been included in line with Medsafe's updated DS requirements
10.	Amendment of the date of revision of text