Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Betagan 0.5% w/v Unit Dose Eye Drops, Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 5.0 mg levobunolol hydrochloride, equivalent to 4.4 mg levobunolol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye Drops, Solution.
A clear, colourless to brown solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the management of patients with ocular hypertension; those with glaucoma of the chronic open angle type, including aphakic patients, those with secondary glaucoma.

4.2 Posology and method of administration

Posology

Adults (including the elderly):
The recommended dosage is one drop of Betagan in the affected eye(s) once or twice daily. Discard product after use.

Paediatric Population
Betagan is not recommended for use in children due to lack of safety and efficacy data (see section 5.1).

Intraocular pressure should be measured approximately four weeks after starting treatment with Betagan as a return to normal ocular pressure can take a few weeks.

Method of administration: topical into the conjunctival sac.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.

Sinus bradycardia, sick sinus syndrome, sino-atrial block second and third-degree atrioventricular block not controlled with a pace maker, overt cardiac failure or cardiogenic shock.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic agents, Betagan is absorbed systemically. Due to the beta-adrenergic component of Betagan, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-blockers may

occur. Incidence of systemic ADRs after topical ophthalmic administration are lower than for systemic administration. To reduce the systemic absorption, see 4.2.

***Cardiac disorders*:** In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to their negative effect on conduction time, beta-blockers should only be given withcaution to patients with first degree atrioventricular block.

***Vascular disorders*:** Patients with severe peripheral circulatory disturbance disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders: Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of levobunolol.

Betagan should be used with caution in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk**.**

Hypoglycaemia/diabetes: Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Beta-blockers may also mask the signs of hyperthyroidism

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

Other beta-blocking agents:The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be exaggerated when levobunolol 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 (see section 4.5).

***Anaphylactic Reactions*:** 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 challenge with such allergens and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

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

Surgical anaesthesia: beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthetist must be informed when the patient is receiving Betagan.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with levobunolol.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data for the use of levobunolol in pregnant women. Levobunolol should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see 4.2.

Epidemiological studies have not revealed malformative effects but 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. If Betagan is administered until delivery, the neonate should be carefully monitored during the first days of life. Animal studies with levobunolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice.

Breast-feeding
Beta-blockers are excreted in breast milk. However, at therapeutic doses of levobunolol in eye drops, it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see 4.2.

If treatment with levobunolol during lactation is considered necessary for the benefit of the mother, consideration should be given to the cessation of breast feeding.

4.7 Effects on ability to drive and use machines

Betagan has minor influence on the ability to drive and use machines. Betagan 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.

4.8 Undesirable effects

Like other topically applied ophthalmic drugs, levobunolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic ADRs after topical ophthalmic administration of beta-blocking agents is lower than for systemic administration.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The following terminologies have been used in order to classify the occurrence of undesirable 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).

The following adverse reactions have been reported with levobunolol:

Psychiatric Disorders
Not known: Depression

Nervous System Disorders
Not known: Confusion, Dizziness, Somnolence, Lethargy, Headache, Insomnia

Eye Disorders
Very Common: Eye irritation, Eye pain

Common: Blepharitis, Conjunctivitis

Not known: Conjunctival/Ocular hyperaemia, Conjuctivitis allergic, Corneal reflex decreased, Iridocyclitis, Keratitis, Vision blurred, Punctate keratitis, Eye/Eyelids pruritus, Eye/Eyelid oedema, Eye discharge, Lacrimation increased, Dry eye, Foreign body sensation in eyes

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: Urticaria, Dermatitis contact (including allergic contact dermatitis), Rash, Erythema of eyelid, Eyelid eczema, Skin exfoliation, Lichenoid keratosis, Pruritus, Alopecia

General Disorders and Administration Site Conditions
Not known: Face oedema, Fatigue/asthenia

Immune System Disorders
Not known: Hypersensitivity reaction including symptoms or signs of eye allergy and skin allergy
Additional adverse reactions have been seen with other ophthalmic beta-blockers and may potentially occur with Betagan:

Eye Disorders: Choroidal detachment following filtration surgery, Corneal erosion, Diplopia, Ptosis
Immune System Disorders: Anaphylactic reaction, Systemic allergic reactions including angioedema
Metabolism and Nutrition Disorders: Hypoglycaemia
Psychiatric disorders: Memory loss, Nightmares
Nervous System Disorders: Cerebral ischemia, Cerebrovascular accident, Increases in signs and symptoms of myasthenia gravis, Paraesthesia
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 (predominantly in patients with pre-existing bronchospastic disease), Cough
Gastrointestinal Disorders: Abdominal pain, Diarrhoea, Dysgeusia, Dry mouth, Dyspepsia, vomiting
Skin and Subcutaneous Tissue Disorders*:* Psoriasiform rash or exacerbation of psoriasis
Musculoskeletal and Connective Tissue Disorders: Myalgia
Reproductive System and Breast Disorders: Decreased libido, Sexual dysfunction

Adverse reactions reported in eye drops containing phosphates:
Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There are no data available on human overdosage with Betagan, which is unlikely to occur via the ocular route. Should accidental ocular overdosage occur, flush the 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 agent should be instituted, such as intravenous administration of atropine sulphate 0.25 to 2 mg to induce vagal blockade. Conventional therapy for hypotension, bronchospasm, heart block and cardiac failure may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Safety and effectiveness of Betagan in paediatric patients have not been established.

Levobunolol is a non-cardioselective beta-adrenoceptor blocking agent, equipotent at both $beta_1$ and $beta_2$ receptors. Levobunolol is greater than 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. Betagan has shown to be as effective as Timolol in lowering intraocular pressure.

Betagan when instilled in the eye will lower elevated intraocular pressure as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure presents a major risk factor in the pathogenesis of glaucomatous field loss. The higher the level of intraocular pressure, the likelihood of optic nerve damage and visual field loss.

The primary mechanism of action of levobunolol in reducing intraocular pressure is most likely a decrease in aqueous humor production. Betagan reduces intraocular pressure with little or no effect on pupil size 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 with the use of Betagan. Patients with cataracts avoid the inability to see around lenticular opacities caused by pupil constriction.

5.2 Pharmacokinetic properties

The onset of action with one drop of Betagan 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.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Poly (vinyl alcohol)
Sodium chloride
Disodium edetate
Sodium phosphate dibasic, heptahydrate
Potassium phosphate monobasic
Sodium hydroxide (to adjust pH) or hydrochloric acid (to adjust pH)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.
The eye drop solution should be used immediately after opening. Any unused solution should be discarded.

6.4 Special precautions for storage

Do not store above 25^{o}C.
Keep the vials in the outer carton in order to protect from light.

6.5 Nature and contents of container

Each pack contains 30 unit dose vials presented in pouched over-wrap material (2 strips of 5 vials per pouch). Each low density polyethylene (LDPE) blow-fill-seal unit dose container (0.9 ml volume) is filled with 0.4 ml solution and has an integral plastic tab bearing the name of the product on one side with the lot number and expiry date on the other.

6.6 Special precautions for disposal and other handling

Ensure that the single dose container is intact before use. Discard any unused solution (i.e. once opened do not re-use container for subsequent doses).

7 MARKETING AUTHORISATION HOLDER

AbbVie Limited
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1824/012/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 October 1993

Date of last renewal: 11 October 2008

10 DATE OF REVISION OF THE TEXT

April 2022