Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Betoptic 0.5% w/v Eye Drops, Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Betaxolol 0.5% w/v (as hydrochloride).

Excipients with known effect: Benzalkonium chloride 0.01% w/v.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.

A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Betoptic is indicated for the reduction of elevated intraocular pressure in patients with ocular hypertension and chronic open angle glaucoma.

4.2 Posology and method of administration

Adults (including the elderly)

The usual dose is one drop to be instilled into the affected eye(s) twice daily.

Children

Betoptic is not recommended for use in children.

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.

After cap is removed, if tamper evident snap collar is loose, remove before using product.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in 6.1.
- Reactive airway disease including severe bronchial asthma or a history of severe bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. Overt cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

For ocular use only

General: Like other topically applied ophthalmic agents, betaxolol is absorbed systemically. Due to the beta-adrenergic component, betaxolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 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 the 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. Treatment with Betoptic should be discontinued at the first signs of cardiac failure.

Due to its negative effect 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 (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 some ophthalmic beta-blockers.

Patients with mild/moderate bronchial asthma, a history of mild/moderate bronchial asthma or, mild/moderate chronic obstructive pulmonary disease (COPD) should be treated with caution.

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

Hyperthyroidism: Beta-adrenergic blocking agents may mask the signs of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, which might precipitate a thyroid storm.

Corneal diseases: In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil. When Betoptic is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

Ophthalmic beta-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 potentiated when betaxolol is given to the 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 anaesthesiologist should be informed when the patient is receiving betaxolol. Consideration may be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anesthesia, because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli.

Myasthenia: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, generalized weakness).

Beta- adrenergic blockade has been reported to unmask or worsen symptoms associated with myasthenia gravis.

Limited clinical experience suggests that the product is suitable for use in aphakic patients.

Contact lenses: Betaxolol eye drops contain benzalkonium chloride which may cause irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of Betaxolol Eye Drops and to wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with betaxolol.

Orally administered beta-adrenergic blocking agents reduce cardiac output in healthy subjects and patients with heart diseases. In patients with severe impairment of myocardial function, beta-adrenergic receptor antagonists may inhibit the sympathetic stimulatory effect necessary to maintain adequate cardiac function.

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

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

Betablockers can decrease the response to adrenaline use to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atophy or anaphylaxis.

If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data on the effects of Betaxolol Eye Drops on human fertility.

Pregnancy

There are no adequate data for the use of betaxolol in pregnant women. Betaxolol should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 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 Betoptic Solution is administered until delivery, the neonate should be carefully monitored during the first days of life.

Lactation

Beta-blockers are excreted in breast milk, having the potential to cause serious undesirable effects in the infant of the nursing mother. However, at therapeutic doses of betaxolol 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 systemic absorption, see section 4.2.

4.7 Effects on ability to drive and use machines

Betoptic 0.5% eye drops, solution has no or negligible influence on the ability to drive and use machines.

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Like other topically applied ophthalmic drugs, betaxolol 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 is lower than for systemic administration. Listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

Summary of the safety profile

In clinical trials with Betaxolol eye drops the most common adverse reaction was ocular discomfort, occurring in 12.0% of patients.

The following adverse reactions have been reported during clinical trials or post marketing surveillance with Betaxolol eye drops and are classified according to the subsequent convention: 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) and frequency unknown/cannot be estimated from the available data.

Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	MedDRA Preferred Term (V 13.0)
Immune system disorders	Frequency unknown: hypersensitivity
Psychiatric disorders	Rare: anxiety, insomnia, depression
Nervous system disorders	Common: headache Rare: syncope Frequency unknown: dizziness
Eye disorders	Very common: ocular discomfort Common: vision blurred, lacrimation increased Uncommon: punctate keratitis, keratitis, conjunctivitis, blepharitis, visual impairment, photophobia, eye pain, dry eye, asthenopia, blepharospasm, eye pruritus, eye discharge, eyelid margin crusting, eye inflammation, eye irritation, conjunctival disorder, conjunctival oedema, ocular hyperaemia Rare: Cataract, madarosis, kerato conjunctivitis sicca Frequency unknown: erythema of eyelid
Cardiac disorders	Uncommon: bradycardia, tachycardia

	Frequency unknown: arrhythmia
Vascular disorders	Rare: hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon: asthma, dyspnoea, rhinitis, Rare: cough, rhinorrhoea
Gastrointestinal disorders	Uncommon: nausea Rare: dysgeusia
Skin and subcutaneous tissue disorders	Rare: dermatitis, rash, alopecia
Musculoskeletal and connective tissue disorders	Rare: muscular weakness, myalgia.
Reproductive system and breast disorders	Rare: libido decreased
General disorders and administration site conditions	Frequency unknown: asthenia

Description of selected adverse reactions

Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with Betoptic Solution:

System Organ Classification	MedDRA preferred term (v 13.0)
Immune system disorders:	*Frequency unknown:* Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylactic reaction.
Metabolism and nutrition disorders:	*Frequency unknown:* Hypoglycaemia.
Psychiatric disorders:	*Frequency unknown:* Nightmares, memory loss.
Nervous system disorders:	*Frequency unknown:* Cerebrovascular accident, cerebral ischemia, increases in signs and symptoms of myasthenia gravis, paraesthesia.
Eye disorders:	*Frequency unknown:* Choroidal detachment following filtration surgery (see 4.4 Special warnings and special precautions for use), decreased corneal sensitivity, corneal erosion, diplopia.
Cardiac disorders:	*Frequency unknown:* Chest pain, palpitations, oedema, congestive heart failure, atrioventricular block, cardiac arrest, cardiac failure.
Vascular disorders:	*Frequency unknown:* Raynaud's phenomenon, cold hands and feet

Respiratory, thoracic, and mediastinal disorders:	*Frequency unknown:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease)
Gastrointestinal disorders:	*Frequency unknown:* dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting.
Skin and subcutaneous tissue disorders:	*Frequency unknown:* Psoriasiform rash or exacerbation of psoriasis
Reproductive system and breast disorders:	*Frequency unknown:* Sexual dysfunction
General disorders and administration site conditions:	*Frequency unknown:* Fatigue

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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

A topical overdose of Betoptic may be flushed from the eye(s) with lukewarm tap water.

In case of accidental ingestion, symptoms of overdose from beta blockage may include bradycardia, hypotension, cardiac failure and bronchospasm.

If overdose with Betaxolol Eye Drops occurs, treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ophthalmologicals: Antiglaucoma Preparation & Miotics.

ATC Code: SO1E D02

Betaxolol, a cardioselective (beta-1-adrenergic) receptor blocking agent, does not have significant membrane-stabilizing (local anaesthetic) activity and is devoid of intrinsic sympathomimetic action.

Orally administered beta-adrenergic blocking agents reduce cardiac output in healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor antagonists may inhibit the sympathetic effect necessary to maintain adequate cardiac function.

Betaxolol has no significant effect on pulmonary function as measured by Forced Expiratory Volume in one second (FEV_1). Forced Vital capacity (FVC), FEV_1/FVC and no evidence of cardiovascular beta-adrenergic-blockade during exercise was observed.

When instilled in the eye, Betaxolol has the action of reducing elevated as well as normal intraocular pressure (IOP), whether or not accompanied by glaucoma. Ophthalmic Betaxolol has little or no effect on the constriction of the pupil minimal effect on pulmonary and cardiovascular parameters.

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. Betaxolol has the action of reducing elevated as well as normal intraocular pressure, and the mechanism of ocular hypotensive action appears to be a reduction of aqueous humour production as demonstrated by tonography and aqueous fluorophotometry.

5.2 Pharmacokinetic properties

Following topical administration, Betaxolol is absorbed systemically. Plasma concentrations of approximately 0.2 ng/ml were detected following administration of Betoptic S Suspension. (Hollo et al., IOVS, vol 47, no 1, pp235-240, 2006).

Betaxolol is highly lipophilic which results in good permeation of the cornea, allowing high intraocular levels of the drug. Betaxolol is characterised by its good oral absorption, low first pass loss and a relatively long half-life of approx 16-22 hours. The elimination of betaxolol is primarily by the renal rather than faecal route. The major metabolic pathways yield two carboxylic acid forms plus unchanged betaxolol in the urine (approx. 16% of the administered dose).

5.3 Preclinical safety data

Reproduction, teratology and peri-and postnatal studies conducted with orally administered betaxolol HCI in rats and rabbits showed evidence of drug-related post-implantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCI was not shown to be teratogenic, however, there were no other adverse effects on reproduction at subtoxic dose levels.

No other preclinical findings were seen that are of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Sodium chloride
Benzalkonium chloride
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years unopened.

After opening, 4 weeks.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

Discard remaining contents 4 weeks after first opening.

6.5 Nature and contents of container

LDPE bottles, with LDPE plug Drop-Tainer and blue polystyrene or polypropylene cap, containing 5 or 10 ml of solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novartis Ireland Limited
Vista Building
Elm Park
Merrion Road
Ballsbridge
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0896/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the first authorisation: 27th August 1986

Date of the last renewal: 27th August 2006

10 DATE OF REVISION OF THE TEXT

July 2018