NEW ZEALAND DATA SHEET

1. PRODUCT NAME

BETOPTIC® (betaxolol hydrochloride) Eye Drops 0.5%

BETOPTIC® S (betaxolol hydrochloride) Eye Drops 0.25%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Betoptic Eye Drops contains betaxolol 5 mg in 1 mL.

Betoptic S Eye Drops contains betaxolol 2.5 mg in 1 mL.

Excipient with known effect

Benzalkonium chloride 0.1 mg in 1 mL (preservative).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Betoptic: eye drops, solution.

Betoptic S: eye drops, suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Betoptic Eye Drops 0.5% and Betoptic S Eye Drops 0.25% have been shown to be effective in lowering intraocular pressure and are indicated in the treatment of ocular hypertension or chronic open angle glaucoma.

Betoptic Eye Drops 0.5% or Betoptic S Eye Drops 0.25% may be used alone or in combination with other IOP-lowering medication.

4.2 Dose and method of administration

NOTE: Shake Betoptic S Eye Drops 0.25% well before use.

The usual dose is one drop of Betoptic Eye Drops 0.5% or Betoptic S Eye Drops 0.25% in the affected eye(s) twice daily. In some patients, the intraocular pressure lowering response to Betoptic Eye Drops 0.5% or Betoptic S Eye Drops 0.25% may require a few weeks to stabilise. Clinical follow up should include a determination of the intraocular pressure during the first month of treatment with Betoptic Eye Drops 0.5% or Betoptic S Eye Drops 0.25%. Thereafter, intraocular pressure should be determined on an individual basis at the judgement of the physician.

Because of diurnal variations of intraocular pressure in individual patients, satisfactory response to twice-a-day therapy is best determined by measuring intraocular pressure at different times during the day. Intraocular pressure ≤ 22 mmHg may not be optimal for control of glaucoma in each patient; therefore, therapy should be individualised.

If the intraocular pressure of the patient is not adequately controlled on this regimen, concomitant therapy with pilocarpine, other miotics, adrenaline or systemically administered carbonic anhydrase inhibitors can be instituted.

When a patient is transferred from several concomitantly administered anti-glaucoma agents, individual adjustment is required. Adjustment should involve one agent at a time made at intervals of not less than one week. A recommended approach is to continue the agents being used and add one drop of Betoptic Eye Drops 0.5% or Betoptic S Eye Drops 0.25% in the affected eye(s) twice a day. On the following day, discontinue one of the other anti-glaucoma agents. The remaining anti-glaucoma agents may be decreased or discontinued according to the patient's response to treatment. The physician may be able to discontinue some or all of the other anti- glaucoma agents.

In order to minimise systemic absorption, apply pressure to the tear duct for two minutes immediately after administration.

Contact Lenses

Neither Betoptic Eye Drops 0.5% nor Betoptic S Eye Drops 0.25% should be instilled while the patient is wearing contact lenses.

If patients continue to wear soft (hydrophilic) contact lenses while under treatment with Betoptic Eye Drops 0.5% or Betoptic S Eye Drops 0.25%, they should remove their lens(es) prior to instilling the drops in the affected eye(s). Lens(es) should not be inserted into the eye(s) until 15 minutes after instillation of the drops.

4.3 Contraindications

Hypersensitivity to any component of this product (refer to Section 6.1).

Betaxolol hydrochloride is contraindicated in patients with sinus bradycardia greater than a first degree block, cardiogenic shock, or patients with a history of overt cardiac failure.

4.4 Special warnings and precautions for use

FOR OCULAR USE ONLY

General

Topically applied beta-adrenergic blocking agents may be absorbed systemically. The same types of cardiovascular and pulmonary and other adverse reactions found with systemic administration of these agents may occur with topical administration. For example, severe respiratory reactions, including death due to exacerbation of bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported with ophthalmic application of beta- adrenergic blocking agents.

Cardiovascular

While ophthalmic betaxolol hydrochloride has been shown to have a minor effect on heart rate and blood pressure in clinical studies, caution should be used in treating patients with a history of cardiac failure or heart block. When beginning therapy with betaxolol patients with a history of severe cardiac disease should be monitored closely for signs of cardiac failure. Treatment with ophthalmic betaxolol hydrochloride should be discontinued at the first sign of cardiac failure.

Because of potential effects of beta-blockers on blood pressure and pulse (e.g. hypotension, bradycardia), use with caution in patients with cerebrovascular insufficiency, untreated phaeochromocytoma or metabolic acidosis, since beta-adrenergic blocking agents can adversely affect such diseases.. If signs or symptoms suggesting reduced cerebral blood flow develop, consider alternative therapy.

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.

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.

Pulmonary

Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. Exacerbation of asthma and bronchospasm have been reported in patients receiving betaxolol treatment. Although rechallenge(s) of some such patients with ophthalmic betaxolol hydrochloride has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta-adrenergic blockers cannot be ruled out.

Diabetes Mellitus

While ophthalmic betaxolol hydrochloride has demonstrated a low potential for systemic effects, beta-adrenergic blocking agents should be used with caution in patients subject to spontaneous hypoglycaemia, or in diabetic patients (especially those with labile diabetes) receiving insulin oral hypoglycaemic agents. Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycaemia.

Major surgery

Consideration should be given to the gradual withdrawal of beta-adrenergic receptor blocking agents prior to general anaesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli.

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.

Muscle weakness

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

Ocular

In patients with angle-closure glaucoma, the immediate treatment objective is to re-open the angle by constriction of the pupil with a miotic agent. Betaxolol has little or no effect on the pupil; therefore, Betoptic Eye Drops 0.5% or Betoptic S Eye Drops 0.25% should be used with a miotic to reduce elevated intraocular pressure in angle-closure glaucoma.

As with other antiglaucoma drugs, diminished responsiveness to ophthalmic betaxolol hydrochloride after prolonged therapy has been reported in some patients. However, in one long- term study in which 250 patients have been followed for up to three years, no significant difference in mean intraocular pressure has been observed after initial stabilisation.

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 eye drops containing betaxolol and wait at least 15 minutes before reinsertion.

Thyrotoxicosis

Beta-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism, e.g. tachycardia. Patients having or suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of these agents which might precipitate a thyroid storm.

Paediatric population

Clinical studies to establish the safety and efficacy in children have not been performed.

4.5 Interaction with other medicines and other forms of interaction

The potential exists for additive systemic and/or intraocular beta blockade effects either on the intraocular pressure or on the known systemic effects of beta blockade for patients receiving a beta-adrenergic receptor blocking agent orally and ophthalmologically or with oral calcium channel blockers, antiarrhythmics (including amiodarone) or digitalis glycosides. Neither Betoptic Eye Drops 0.5% nor Betoptic S Eye Drops 0.25% should be used in conjunction with other topical beta-blocking agents. Coadministration of ophthalmic beta-blockers with digitalis may have additive effects in prolonging atrioventricular conduction time.

Although betaxolol hydrochloride used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with betaxolol hydrochloride and adrenaline has been reported occasionally.

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia which may result in vertigo, syncope, or postural hypotension. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs.

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

Caution should be used where a beta-2-agonist is administered concurrently with a beta-blocker. When used in conjunction with topical miotics and/or systemically administered carbonic anhydrase inhibitors, the effect of betaxolol eye drops in lowering IOP may be additive.

Ophthalmic beta-blockers and phenothiazone compounds may have potential additive hypotensive effects due to mutual inhibition of metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C

There have been no adequate and well controlled studies in pregnant women. Studies in animals have shown reproductive toxicity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly indicated. Betaxolol is not recommended during pregnancy.

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.

Beta-adrenergic receptor blocking agents may cause bradycardia in the fetus and newborn infant. During the final part of pregnancy and parturition these drugs should, therefore, only be given after weighing the needs of the mother against the risk to the fetus. If betaxolol eye drops is administered until delivery, the neonate should be carefully monitored during the first days of life

Breast-feeding

It is not known whether ophthalmic betaxolol hydrochloride is excreted in human milk following topical ocular administration. However, a risk to the suckling child cannot be excluded.

Betaxolol concentrations in milk following oral administration may be up 3 times those in maternal blood, having the potential to cause serious undesirable effects in the infant of the nursing mother.

While it is unlikely that clinically important doses of the drug would be absorbed by breast-fed infants during ophthalmic use in women, caution should be exercised when ophthalmic betaxolol hydrochloride is prescribed for breast-feeding women.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from betaxolol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

As with any eye drop, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines.

If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Ocular

In clinical trials the most frequent event associated with the use of ophthalmic betaxolol hydrochloride has been transient ocular discomfort. The incidence of discomfort was 16% in patients treated with Betoptic S Eye Drops 0.25% and 25% in patients treated with Betoptic Eye Drops 0.5%. Decreased corneal sensitivity, erythema, itching sensation, corneal punctate keratitis, anisocoria, blurred vision, foreign body sensation, tearing, dryness of eyes, inflammation, discharge, ocular pain, decreased visual acuity, crusty lashes and photophobia have been reported in up to 4% of patients.

Systemic

Systemic reactions following topical administration of Betoptic Eye Drops 0.5% or Betoptic S Eye Drops 0.25% have been reported rarely.

These include:

Cardiovascular	Bradycardia, heart block and congestive failure.
Pulmonary	Pulmonary distress characterised by dyspnoea, bronchospasm, thickened bronchial secretions, asthma and respiratory failure.
Central Nervous System	Insomnia, dizziness, vertigo, headaches, depression, lethargy and an increase in signs and symptoms of myasthenia gravis.
Other	Hives, toxic epidermal necrolysis, hair loss, glossitis.

Post Marketing Experience

Since topically applied beta-adrenergic blocking agents may be absorbed systemically, adverse reactions found with systemic administration of beta1-adrenergic blocking agents may occur with topical administration. These may include bradycardia, a slowed AV (atrioventricular) - conduction or increase of an existing AV-block, hypotension, heart failure, cold and cyanotic extremities, Raynauds phenomenon, paraesthesia of the extremities, increase of an existing intermittent claudication, fatigue, headaches, impaired vision, hallucinations, psychoses, confusion, impotence, dizziness, sleep disturbances, depression, nightmares, gastro-intestinal problems, nausea, vomiting, diarrhoea, bronchospasm in patients with bronchial asthma or a history of asthmatic complaints, disorder of the skin, especially rash, and dry eyes. Beta blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.

The following adverse reactions are classified according to the following 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), or not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions were obtained from clinical trials and post marketing spontaneous reports.

Eye disorders

Very Common (≥ 10%): ocular discomfort.

Common (≥ 1% to < 10%): vision blurred, lacrimation increased, foreign body sensation in eyes.

Uncommon (≥ 0.1% to < 1%): punctate keratitis, keratitis, conjunctivitis, blepharitis, visual acuity reduced, visual impairment, photophobia, eye pain, dry eye, asthenopia, blepharospasm, abnormal sensation in eye, eye pruritus, eye discharge, eyelid margin crusting, eye inflammation, eye irritation, conjunctival disorder, conjunctival oedema, ocular hyperaemia.

Rare (≥ 0.01% to < 0.1%): cataract, refraction disorder, eye disorder.

Not Known: erythema of eyelid.

Cardiac disorders

Uncommon (≥ 0.1% to < 1%): bradycardia, tachycardia.

Not Known: arrhythmia.

Vascular disorders

Rare (≥ 0.01% to < 0.1%): hypotension.

Nervous system disorders

Common (≥ 1% to < 10%): headache.

Rare (≥ 0.01% to < 0.1%): syncope.

Not Known: dizziness.

Psychiatric disorders

Rare (≥ 0.01% to < 0.1%): anxiety.

Not Known: insomnia, depression.

Immune system disorders

Not Known: hypersensitivity.

Respiratory, thoracic and mediastinal disorders

Uncommon (≥ 0.1% to < 1%): asthma, dyspnoea, respiratory disorder, rhinitis.

Rare (≥ 0.01% to < 0.1%): cough, rhinorrhea.

Gastrointestinal disorders

Uncommon (≥ 0.1% to < 1%): nausea.

Rare (≥ 0.01% to < 0.1%): dysgeusia.

Skin and subcutaneous tissue disorders

Rare (≥ 0.01% to < 0.1%): dermatitis, rash.

Not Known: periorbital oedema, alopecia.

Infections and infestations

Rare (≥ 0.01% to < 0.1%): influenza, infection, bronchitis, sinusitis.

Reproductive system and breast disorders

Rare (≥ 0.01% to < 0.1%): libido decreased.

Surgical and medical procedures

Rare (≥ 0.01% to < 0.1%): antral lavage.

General disorders and administration site conditions

Not Known: asthenia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting.

4.9 Overdose

No information is available on overdosage of humans. The oral LD50 of the drug ranged from 350-920 mg/kg in mice and 860-1050 mg/kg in rats. The symptoms which might be expected with an overdose of a systemically administered beta-1-adrenergic receptor blocking agent are bradycardia, hypotension and acute cardiac failure.

A topical overdose of Betoptic Eye Drops 0.5% or Betoptic S Eye Drops 0.25% may be flushed from the eye(s) with warm water or normal saline (sodium chloride solution 0.9%). If accidentally ingested, efforts to decrease further absorption may be appropriate (gastric lavage). The most common signs and symptoms of overdosage from systemic beta-blockers are bradycardia, hypotension, bronchospasm, and acute cardiac failure. If these occur, discontinue therapy and initiate appropriate supportive therapy.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Ophthalmologicals - Antiglaucoma Preparations and Miotics.
ATC Code: S01E D02.

Mechanism of action

When instilled in the eye, Betoptic Eye Drops 0.5% and Betoptic S Eye Drops 0.25% have the action of reducing elevated intraocular pressure as well as normal intraocular pressure, whether or not accompanied by glaucoma.

Optic nerve head damage and visual field loss are a result of a sustained elevated intraocular pressure and poor ocular perfusion. The ocular hypotensive action of betaxolol appears to be mediated by a reduction of aqueous production as demonstrated by tonography and aqueous fluorophotometry. The onset of action with betaxolol can generally be noted within 30 minutes and the maximal effect can usually be detected 2 hours after topical administration. A single dose provides a 12-hour reduction in intraocular pressure.

Betaxolol has little or no effect on pupil size and does not produce accommodative spasm which are frequently seen with miotic agents. The blurred vision and night blindness often associated with standard miotic therapy are not associated with Betoptic Eye Drops 0.5% or Betoptic S Eye Drops 0.25%. Thus, patients with central lenticular opacities avoid the visual impairment caused by a constricted pupil.

Pharmacodynamic effects

Betaxolol hydrochloride is a cardioselective (beta-1-adrenergic) receptor blocking agent. 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 stimulatory effect necessary to maintain adequate cardiac function.

In clinical pharmacology studies ophthalmic betaxolol has minimal effect on pulmonary and cardiovascular parameters.

Ophthalmic betaxolol hydrochloride solution at 1% (one drop in each eye) was compared to placebo in a three-way masked, crossover study challenging nine patients with reactive airway disease1. Betaxolol hydrochloride has no significant effect on pulmonary function as measured by Forced Expiratory Volume in one second (FEV1), Forced Vital Capacity (FVC) and FEV1/FVC. Additionally, the action of isoprenaline, a beta stimulant, administered at the end of the study was not inhibited by ophthalmic betaxolol hydrochloride. In contrast, ophthalmic timolol significantly decreased these pulmonary functions.

FEV1 - PERCENT CHANGE FROM BASELINE1			
Means			
	Betaxolol 1%[a]	Timolol 0.5%	Placebo
Baseline	1.6	1.4	1.4
60 minutes	2.3	-25.7*	5.8
120 minutes	1.6	-27.4*	7.5
240 minutes	-6.4	-26.9*	6.9
Isoprenaline[b]	36.1	-12.4*	42.8

[1.]Schoene RB *et al*., Am J Ophthal, 97, 86-92, 1984.

[a.] Twice the clinical concentration.

[b.] Inhaled at 240 minutes; measurement at 270 minutes.

* Timolol statistically different from betaxolol and placebo ($p<0.05$).

No evidence of cardiovascular beta adrenergic-blockade during exercise was observed with betaxolol in a double-masked, crossover study in 24 normal subjects comparing ophthalmic betaxolol hydrochloride solution 1.0% and placebo for effects on blood pressure and heart rate[2]. Mean arterial blood pressure was not affected by any treatment; however, ophthalmic timolol produced a significant decrease in the mean heart rate.

MEAN HEART RATES[2]			
Bruce Stress Exercise Test Minutes	Treatment		
	[a]	Timolol 0.5%	Placebo
0	79.2	79.3	81.2
2	130.2	126.0	130.4
4	133.4	128.0*	134.3
6	136.4	129.2*	137.9
8	139.8	131.8*	139.4
10	140.8	131.8*	141.3

[2] Atkins JM *et al*., Am J Ophthal, 99, 173-175, 1985.

[a] Twice the clinical concentration.

* Mean heart rate significantly lower for timolol than betaxolol or placebo ($p<0.05$).

Clinical efficacy and safety

In controlled, double-masked studies, the magnitude and duration of the ocular hypotensive effect of Betoptic Eye Drops 0.5% and Betoptic S Eye Drops 0.25% were clinically equivalent. Betoptic S Eye Drops 0.25% were significantly more comfortable than Betoptic Eye Drops 0.5%.

Clinical studies show that topical betaxolol reduces mean intraocular pressure 25% from baseline. In trials using 22 mmHg as a generally accepted index of intraocular pressure control, betaxolol hydrochloride solution was effective in more than 94% of the population studied, of which 73% were treated with the beta blocker alone. In controlled, double-masked studies, the magnitude and duration of the ocular hypotensive effect of Betoptic Eye Drops 0.5% and ophthalmic timolol were clinically equivalent.

Clinical observation of glaucoma patients treated with betaxolol hydrochloride solution for up to three years shows that the intraocular pressure lowering effect is well maintained.

Ophthalmic betaxolol hydrochloride has also been used successfully in glaucoma patients who have undergone a laser trabeculoplasty and have needed additional long term ocular hypotensive therapy. Ophthalmic betaxolol hydrochloride has been well-tolerated in glaucoma patients wearing hard or soft contact lenses (See Section 4.2 Dose and method of administration, Contact Lenses) and in aphakic patients.

5.2 Pharmacokinetic properties

Pharmacokinetics

Not available.

5.3 Preclinical safety data

Ocular anaesthesia has been observed in rabbit studies.

Carcinogenicity

Lifetime studies with betaxolol hydrochloride have been completed in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at 3, 12 or 48 mg/kg/day; betaxolol hydrochloride demonstrated no carcinogenic effect.

Mutagenicity

In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol hydrochloride was non-mutagenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betoptic Eye Drops 0.5%

Benzalkonium chloride (as a preservative)

Disodium edetate

Sodium chloride

Purified water.

Betoptic S Eye Drops 0.25%

Benzalkonium chloride (as a preservative)

Mannitol

Polystyrene sulfonate hydrogen

Carbomer 934P

Disodium edetate

Purified water.

6.2 Incompatibilities

Unknown.

6.3 Shelf life

Betoptic

36 months.

Betoptic S

24 months.

6.4 Special precautions for storage

Store below 25° C.

Store the bottle in the outer carton.

Discard container 4 weeks after opening.

6.5 Nature and contents of container

Bottle dropper (Drop-Tainer®).

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Only bMedicine.

8. SPONSOR

Novartis New Zealand Limited

109 Carlton Gore Road

Newmarket

Auckland 1023.

PO Box 99102

Newmarket

Auckland 1149

New Zealand.

Free Phone: 0800 354 335.

9. DATE OF FIRST APPROVAL

Betoptic: 19 June 1986.

Betoptic S: 11 April 1991.

10. DATE OF REVISION OF THE TEXT

21 September 2017.

Summary Table of Changes

All sections	Updated to Summary of Product Characteristics format
8. Sponsor	Change in sponsor from Pharmaco to Novartis

REFERENCES

1. Schoene RB *et al*., Am J Ophthal, 97, 86-92, 1984.
2. Atkins JM *et al*., Am J Ophthal, 99, 173-175, 1985.

® Registered Trademark.