BETOPTIC® S

0.25% Eye Drops **Suspension**
(betaxolol)

1. NAME OF THE MEDICINAL PRODUCT

BETOPTIC®S 0.25 %, Eye Drops

Suspension

2. QUALITATIVE AND QUANTITIVE COMPOSITION

1 ml of Suspension contains 2.5 mg betaxolol base (equivalent to 2.8 mg betaxolol hydrochloride)
Preservative : 1 ml suspension contains 0.1 mg benzalkonium chloride

Excipients: Mannitol, Poly(styrene-divinylbenzene) Sulfonic Acid, Carbomer 974P, Disodium Edetate, Benzalkonium chloride N-lauroylsarcosine, Boric Acid, Concentrated Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH) and Purified Water

3. PHARMACEUTICAL FORM

Eye Drops, Suspension
white to off-white sterile suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BETOPTIC® S Suspension contains betaxolol, a cardioselective beta-adrenergic receptor blocking agent (beta-blocker).
BETOPTIC® S Suspension is indicated for the reduction of elevated intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

4.2 Posology and method of administration

Posology
Use in adults
The recommended dose is 1 or 2 drops of BETOPTIC® S Suspension in the affected eye(s) twice daily. In some patients, the intraocular pressure lowering responses to BETOPTIC S Suspension may require a few weeks to stabilise. As with any new medication, careful monitoring of patients is advised.

If the intraocular pressure of the patient is not adequately controlled on this regimen, concomitant therapy with other anti-glaucoma agents can be instituted.

When a patient is transferred from a single anti-glaucoma agent, continue the agent already used and add 1 drop of BETOPTIC S suspension in the affected eye(s) twice a day. On the following day, discontinue the previous anti-glaucoma agent completely and continue with BETOPTIC S suspension.

When a patient is transferred from several concomitantly administered anti-glaucoma agents, individualisation is required. Adjustment should involve 1 agent at a time made at intervals of not less than 1 week.

Use in pediatric patients (below 18 years)
Limited clinical data are available regarding the safety and efficacy of Betoptic 0.25% in pediatric patients.

Use in patients with renal or hepatic impairment
Safety and efficacy in patients with renal or hepatic impairment have not been studied.

Use in geriatric patients (65 years or above)
No overall differences in safety or efficacy have been observed between elderly and younger adult patients.

Method of administration
For ocular use only.
Shake well before use.

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

To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye. Patients should be instructed to keep the bottle tightly closed when not in use.
Nasolacrimal occlusion and closing the eyelids for 2 minutes after instillation is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse drug reactions.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.

- Sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure, or cardiogenic shock.

4.4 Special warnings and precautions for use

General

- Like other topically applied ophthalmic agents, betaxolol is absorbed systemically. Due to the beta-blocking component in ophthalmic betaxolol, the same types of cardiovascular, pulmonary and other adverse drug reactions seen with systemic beta-adrenergic blocking agents may occur.

Cardiac disorders

- BETOPTIC S Suspension has been shown to have a minor effect on heart rate and blood pressure in clinical studies.

- 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 adverse drug reactions. Treatment with BETOPTIC S Suspension should be discontinued at the first signs of cardiac failure.

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.

- Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. There have been reports of asthmatic attacks and pulmonary distress during betaxolol treatment. Although rechallenges of some such patients with ophthalmic betaxolol has not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta-blockers cannot be ruled out.

Hyperglycemia/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-blockers may mask the signs of hyperthyroidism (e.g. tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockers, which might precipitate a thyroid storm.

Muscle Weakness

- Beta-blockers have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness).

Other beta-blockers

- The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when betaxolol is given to the patients already receiving a systemic beta-blocker. The response of these patients should be closely observed. The use of two topical beta-blockers 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 reactions 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 anesthesia

- Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g., of adrenaline. The anesthesiologist should be informed if the patient is receiving BETOPTIC S suspension.

- Consideration should 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.

Ocular

- When BETOPTIC® S Suspension is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone. 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.

Contact lenses

- BETOPTIC® S Suspension contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Patients should avoid contact with soft contact lenses. In case patients are allowed to wear contact lenses, they must be instructed to remove contact lenses prior to application of BETOPTIC® S Suspension and wait at least 15 minutes before reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

- There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers are administered concomitantly with oral calcium channel blockers, beta-blockers, catecholamine-depleting drugs (such as reserpine), antiarrhythmics (including amiodarone), digitalis glycosides or adrenergic psychotropic drugs.

- There is a potential additive effect on the intraocular pressure when BETOPTIC®S Suspension is administered concomitantly with oral beta-blockers.

- Beta-blockers can decrease the response to adrenaline used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy or anaphylaxis (see section 4.4 Special warnings and precautions for use).

4.6 Fertility, Pregnancy and lactation

Pregnancy

Risk summary
There are no adequate data and well-controlled studies in pregnant women regarding the ocular use of BETOPTIC® S Suspension.
Epidemiological studies have not revealed malformative effects but show a risk for intra-uterine growth retardation when beta-blockers are administered orally. In addition, signs and symptoms of beta-blockade (e.g., bradycardia, hypotension, respiratory distress and hypoglycemia) have been observed in the neonate when systemic beta-blockers have been administered to the mother until delivery.

Studies in rats and rabbits with betaxolol have shown embryo-fetal toxicitiy.

BETOPTIC® S Suspension should not be used during pregnancy unless clearly necessary. However, if BETOPTIC® S Suspension is administered during pregnancy up to the time of delivery, the neonate should be carefully monitored during the first days of life.

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

Lactation

Risk summary
There is limited data regarding the use of BETOPTIC® S Suspension in breast-feeding women.

It is not known whether betaxolol is transferred into human milk following topical ocular administration. Betaxolol is transferred into human milk following oral administration. Oral beta-blockers have the potential to cause serious adverse drug reactions in the breast-fed infant. However, in the case of ocular administration of betaxolol at therapeutic doses, it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for BETOPTIC® S Suspension and any potential adverse effects on the breast-fed child from BETOPTIC® S Suspension.

Fertility

There are no data on the effects of BETOPTIC® S Suspension on human fertility.

4.7 Effects on ability to drive and use machines

BETOPTIC S suspension 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

The following adverse reactions are classified according to the 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). Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been reported during clinical trials and identified from post-marketing surveillance.

System Organ Classification	Adverse drug reactions
Immune system disorders	*Not known* : hypersensitivity
Psychiatric disorders	*Rare* : anxiety, depression *Not known* : insomnia

Nervous system disorders	Common : headache *Rare* : syncope, vertigo, lethargy, myasthenia gravis, parosmia *Not known* : 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, N*ot known* : erythema of eyelid
Cardiac disorders	*Uncommon* : bradycardia, tachycardia *Rare* : atrioventricular block, cardiac failure congestive Not known: arrhythmia
Vascular disorders	*Rare*: hypotension
Respiratory, thoracic and mediastinal disorders	*Uncommon* : asthma, dyspnoea, rhinitis *Rare* : cough, rhinorrhoea, bronchospasm, increased viscosity of bronchial secretion
Gastrointestinal disorders	*Uncommon* : nausea *Rare* : glossitis, dysgeusia
Skin and subcutaneous tissue disorders	*Rare* : dermatitis, rash, urticaria, toxic epidermal necrolysis Not known: alopecia
Reproductive system and breast disorders	*Rare*: Libido decreased
General disorders and administration site conditions	Not known: asthenia

Additional medical events reported with other formulations of betaxolol include hypoaesthesia eye, corneal staining which may appear in dendritic formations, oedema and pupils unequal.

4.9 Overdose

An ocular overdose of BETOPTIC® S Suspension may be flushed from the eye(s) with lukewarm tap water.

In case of accidental ingestion, symptoms of overdose from beta-blockade may include bradycardia, hypotension, cardiac failure and bronchospasm.
If overdose with BETOPTIC® S Suspension occurs, treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : anti-glaucoma preparations and miotics, beta-blocking agents
ATC code : S 01 ED 02

Mechanism of action

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

Elevated intraocular pressure (IOP) is 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. Upon instillation in the eye, BETOPTIC® S Suspension reduces elevated as well as normal IOP, whether or not accompanied by glaucoma. The mechanism of ocular hypotensive action appears to be a reduction of aqueous production.The onset of action with BETOPTIC® S Suspension can generally be noted within 30 minutes and the maximal effect can be usually noted at 2 hours after topical administration. A single dose provides a 12-hour reduction in intraocular pressure.

BETOPTIC® S Suspension's action as a neuroprotective agent has been shown in both in vivo and in vitro experiments in rabbit retina, rat cortical cultures and chick retinal cultures.

Pharmacodynamic effects

The polar nature of betaxolol can produce apparent ocular irritation. In the current formulation, molecules are ionically bound to the amberlite resin. Upon instillation, these molecules are displaced by sodium ions in the tear film. This displacement process occurs over several minutes and enhances the ocular comfort. BETOPTIC® S Suspension has little or no effect on the constriction of the pupil.

The peripheral vasorelaxing action of BETOPTIC® S Suspension has been shown in an *in vivo* study in dogs, while the vasorelaxing and calcium channel blocking actions of BETOPTIC® S Suspension have been demonstrated in several *in vivo* studies utilizing both non-ocular and ocular vessels from rat, guinea pig, rabbit, canine, porcine and bovine models.

BETOPTIC® S Suspension may be absorbed systemically possibly causing the same adverse drug reactions as the orally administered drug. Oral beta-blockers reduce cardiac output in healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-blockers may inhibit the sympathetic stimulatory effect necessary to maintain adequate cardiac function.

No evidence of cardiovascular beta-blockade during exercise was observed in a double-masked, cross-over study in 24 normal subjects comparing ophthalmic BETOPTIC® S Suspension and placebo for effects on blood pressure and heart rate.

Clinical Safety and Efficacy

In controlled, double-masked studies, the magnitude and duration of the ocular hypotensive effect of BETOPTIC® S Suspension 0.25% and0.5 % were clinically equivalent..

Data obtained during controlled clinical trials in patients with chronic open-angle glaucoma and ocular hypertension indicates that treatment with BETOPTIC® S Suspension has a superior long-term benefit on the visual field as compared to treatment with timolol, a non-selective beta-blocker. In three-way masked crossover studies comparing ophthalmic BETOPTIC® S Suspension to timolol and placebo, BETOPTIC® S Suspension was found to have minimal effect on pulmonary and cardiovascular parameters. In contrast, timolol significantly decreased pulmonary function and produced a lowering of the mean heart rate. Ophthalmic betaxolol solution at 1 % (one drop in each eye) was compared to placebo in a cross-over study challenging nine patients with reactive airway disease. Betaxolol had no significant effect on pulmonary function as measured by the Forced Expiratory Volume per Second (FEV1), the Forced Vital Capacity (FVC) and the relation between them (FEV1 / FVC) and was not significantly different from placebo. The action of isoproterenol, a beta-stimulant, administered at the end of the study was not inhibited by ophthalmic betaxolol. Additionally, during therapy with BETOPTIC® S Suspension, no negative effect on the blood supply to the optic nerve has been observed. Rather, BETOPTIC® S Suspension maintained or improved ocular blood flow / perfusion.

BETOPTIC® S Suspension does not produce miosis or accommodative spasm, as frequently seen with miotic agents. The blurred vision and night blindness often associated with standard miotic therapy are not associated with ophthalmic BETOPTIC® S Suspension. Thus, patients with central lenticular opacities avoid the visual impairment caused by a constricted pupil. BETOPTIC® S Suspension has been used successfully in glaucoma patients who have undergone laser trabeculoplasty and have needed additional long-term hypotensive therapy. BETOPTIC® S Suspension has also been well tolerated in glaucoma patients wearing hard or soft contact lenses and in aphakic patients.

BETOPTIC® S Suspension's action as a neuroprotective agent has been shown in both in vivo and in vitro experiments in rabbit retina, rat cortical cultures and chick retinal cultures.

Pharmacokinetic properties Absorption

Plasma exposure to betaxolol is low following topical ocular administration. Following topical ocular administration of 0.5% Betoptic solution to normal volunteers for 1 week, maximum steady-state plasma drug concentrations were about 1 ng/ml or less.

Distribution

Betaxolol is highly lipophilic which results in good permeation of the cornea, allowing high intraocular levels of the drug.

Metabolism

In humans, betaxolol is primarily metabolized to two carboxylic acid derivatives: one formed by elimination of the cyclopropyl-methyl group and hydroxylation of the remaining terminal carbon followed by oxidation of this alcohol (24% of dose), the other formed by oxidation of the carbon α to the isopropyl-amino moiety, with elimination of the latter (35% of dose). Phase II metabolism of betaxolol and its metabolites by conjugation reactions is negligible.

Excretion

Betaxolol is eliminated primarily in the urine (80-90% of dose), with 16% of the dose as parent drug and the remainder being the two primary metabolites and small amounts of minor metabolites.

5.2 Preclinical safety data

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

In a variety of in vitro and in vivo bacterial and mammalian cell assays, betaxolol hydrochloride was nonmutagenic.

Effects in non-clinical reproductive toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

No preclinical studies have been conducted to specifically address risks related to administration to juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

Not applicable.

6.2 Special precautions for storage

Keep the bottle in the outer carton. Store upright at or below 30°C..
Do not use this medicine after the expiry date which is stated on the packaging.
Discard 4 weeks after first opening.
Keep this medicine out of the sight and reach of children.

6.3 Nature and contents of container

Plastic bottle Dispensers containing 5 ml

6.4 Special precautions for disposal

No special requirements.

6.5 Manufacturer
See folding box

Novartis Pharma AG, Basel, Switzerland