## 1. NAME OF THE MEDICINAL PRODUCT

# BETOPTIC*S

0.25% eye drops, suspension
(betaxolol)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

## 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 has been shown to be effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma and ocular hypertension. It may be used alone or in combination with other intraocular pressure lowering medications.

### 4.2 Posology and method of administration

**Posology**

Use in adults (including the elderly)

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.

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.

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 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 children

- Clinicians should strongly evaluate the risks and benefits when considering medical therapy with BETOPTIC S suspension in paediatric patients. A detailed paediatric history and examination to determine possible systemic abnormalities should precede the use of BETOPTIC S suspension. No specific dosage recommendation can be given as there is only limited clinical data. However, if the benefit outweighs the risk, it is recommended to use the lowest active agent concentration available once daily. If intraocular pressure cannot be sufficiently controlled, a careful up titration to a maximum of 2 drops daily per affected eye has to be considered. If applied twice daily, an interval of 12 hours is recommended.
- Patients, especially neonates, should be strongly observed after the first dose for 1 or 2 hours in the clinic and closely monitored for ocular and systemic side effects until surgery is performed.

Use in patients with hepatic or renal impairment

BETOPTIC S suspension has not been studied in patients with renal or hepatic disease.

**Method of administration**

For ocular use.
Shake well before use.

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

To prevent contamination of the dropper tip and suspension, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip. Keep the bottle tightly closed when not in use.

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.

If more than one topical ophthalmic product is being used, the products 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 listed in section 6.1.
- 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, betaxolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-blockers 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 of adverse 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.

**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.

**Hyperthyroidism**

- Beta-blockers may also 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 generalised 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 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 BETOPTIC* S suspension.
- Consideration should be given to the gradual withdrawal of beta-blockers prior to general anaesthesia 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 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 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.

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**

There are no adequate data for the use of betaxolol in pregnant women.
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.

BETOPTIC S suspension should not be used during pregnancy unless clearly necessary. However, if BETOPTIC S suspension is administered until delivery, the neonate should be carefully monitored during the first days of life.

**Breast-feeding**

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.

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

**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 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), 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 have been reported during clinical trials and identified from post-marketing surveillance.

| System Organ Classification | Adverse reactions |
|---|---|
| Immune system disorders | *Not known:* hypersensitivity |
| Psychiatric disorders | *Rare:* anxiety, depression<br>*Not known:* insomnia |
| Nervous system disorders | *Common:* headache<br>*Rare:* syncope, myasthenia gravis, lethargy , vertigo, parosmia<br>*Not known:* dizziness |

| System Organ Classification | Adverse reactions |
|---|---|
| Eye disorders | *Very Common:* ocular discomfort<br>*Common:* vision blurred, lacrimation increased<br>*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<br>*Rare:* cataract<br>*Not known:* erythema of eyelid |
| Cardiac disorders | *Uncommon:* bradycardia, tachycardia<br>*Rare:* atrioventricular block, cardiac failure congestive<br>*Not known:* arrhythmia |
| Vascular disorders | *Rare:* hypotension |
| Respiratory, thoracic and mediastinal disorders | *Uncommon:* asthma, dyspnoea, rhinitis<br>*Rare:* bronchospasm, cough, increased viscosity of bronchial secretion, rhinorrhoea |
| Gastrointestinal disorders | *Uncommon:* nausea<br>*Rare:* glossitis, dysgeusia |
| Skin and subcutaneous tissue disorders | *Rare:* toxic epidermal necrolysis, rash, urticaria, dermatitis<br>*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.

**Paediatric population**

The safety and IOP-lowering effect of BETOPTIC* S suspension has been demonstrated in paediatric patients in a 3-month, multi-centre, double-masked, active-controlled trial. The adverse drug reaction profile of BETOPTIC S suspension was comparable to that seen in adult patients.

### 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: antiglaucoma preparations and miotics, beta-blocking agents. ATC code: S01ED02.

**Mechanism of action**

Betaxolol hydrochloride, a cardioselective (beta-1-adrenergic) receptor blocking agent, does not have significant membrane-stabilizing (local anaesthetic) 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, betaxolol 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 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'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 eye drops, suspension 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.

The peripheral vasorelaxing action of betaxolol has been shown in an *in vivo* study in dogs, while the vasorelaxing and calcium channel blocking actions of betaxolol 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. Betaxolol causes local constriction of the ciliary arterioles of rabbits (decreasing after administration during 50 days).

Betaxolol may be absorbed systemically possibly causing the same undesirable effects 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 betaxolol 1% 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 betaxolol 0.25% eye drops, suspension and betaxolol 0.5% eye drops, solution were clinically equivalent.
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 was effective in more than 94% of the population studies, of which 73% were treated with the beta-blocker alone. Data obtained during controlled clinical trials in patients with chronic open-angle glaucoma and ocular hypertension indicates that treatment with betaxolol 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 betaxolol to timolol and placebo, betaxolol 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.
Ophthalmic betaxolol has minimal effect on pulmonary and cardiovascular parameters. Additionally, during therapy with betaxolol, no negative effect on the blood supply to the optic nerve has been observed. Rather, betaxolol maintained or improved ocular blood flow/perfusion. Clinical observation of glaucoma patients treated with betaxolol for up to 3 years shows that the intraocular pressure lowering effect is well maintained.

Betaxolol 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 betaxolol. Thus, patients with central lenticular opacities avoid the visual impairment caused by a constricted pupil. Betaxolol has been used successfully in glaucoma patients who have undergone laser trabeculoplasty and have needed additional long-term hypotensive therapy. Betaxolol has also been well tolerated in glaucoma patients wearing hard or soft contact lenses and in aphakic patients.

**Paediatric population**

Betaxolol eye drops, suspension 0.25% was effective in reducing intraocular pressure in a clinical trial including 35 paediatric patients on treatment. In a published randomized paediatric clinical trial, betaxolol eye drops, suspension 0.25% (N=34) produced statistically significant reductions in intraocular pressure in paediatric glaucoma patients dosed twice daily.

### 5.2 Pharmacokinetic properties

**Absorption**

Following oral or i.v. administration, betaxolol plasma concentrations decline with a terminal half-life of 15 to 16 hours. Oral bioavailability is about 80%. Following a 20 mg oral dose, a mean maximum plasma concentration of about 46 ng/ml was achieved at 4 hours. Plasma drug levels increase in a dose-proportional manner with increasing dose.

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

**Distribution**

Following multiple topical ocular doses to pigmented rabbits, highest ocular exposure was observed in aqueous humor, iris-ciliary body and retina with mean maximum steady-state concentrations of 776, 32500 and 18 ng/g, respectively. Exposure in retina and other posterior tissues was shown to arise from both local absorption and redistribution from the systemic circulation. Plasma drug levels were low (3 ng/ml or less).

**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 $\alpha$ 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.

### 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on onventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

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

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.

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.

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of 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

### 6.2 Incompatibilities

Not applicable.

### 6.3 Special precautions for storage

Store upright at room temperature (8°C-30°C). Keep the bottle in the outer carton.
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.

### 6.4 Nature and contents of container

Plastic DROPTAINER* dispenser containing 5 ml.

### 6.5 Special precautions for disposal

No special requirements.

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