1. NAME OF THE MEDICINAL PRODUCT

BETOPTIC* 0.5% sterile ophthalmic solution
(betaxolol)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 5 mg betaxolol base (equivalent to 5.6 mg betaxolol hydrochloride).
Preservative: 1 ml of solution contains 0.1 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile ophthalmic solution.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BETOPTIC* ophthalmic solution contains betaxolol, a cardioselective beta-adrenergic receptor blocking agent (beta-blocker).

BETOPTIC ophthalmic solution has been shown to be effective in lowering intraocular pressure and is indicated in the treatment of:
- patients with chronic open-angle glaucoma
- patients with elevated intraocular pressure (ocular hypertensive patients)
- patients with glaucoma or ocular hypertension who have reactive airway disease
- patients with glaucoma or ocular hypertension who are currently on multiple-anti-glaucoma therapy.

4.2 Posology and method of administration

Posology
Use in adults (including the elderly)
The usual dose is 1 drop of BETOPTIC ophthalmic solution in the affected eye(s) twice daily. In some patients, the intraocular pressure lowering response to BETOPTIC ophthalmic solution 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 ophthalmic solution. Thereafter, intraocular pressures should be determined on an individual basis at the judgement of the physician.

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

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
The safety and efficacy of BETOPTIC ophthalmic solution in children have not been established.

Use in patients with hepatic or renal impairment
BETOPTIC ophthalmic solution has not been studied in patients with renal or hepatic disease.

Method of administration
For ocular use.

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

To prevent contamination of the dropper tip and solution, 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
- 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.

Respiratory disorders
- Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.
- BETOPTIC ophthalmic solution, a cardioselective beta-blocker, has produced only minimal effects in patients with reactive airway disease. Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function.

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.

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 ophthalmic solution.
- 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 ophthalmic solution 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.
- As with the use of other anti-glaucoma drugs, diminished responsiveness to BETOPTIC ophthalmic solution 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 stabilization.

Contact lenses
- BETOPTIC ophthalmic solution 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 ophthalmic solution 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 solution is 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 ophthalmic solution 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.
- Although BETOPTIC ophthalmic solution used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with BETOPTIC ophthalmic solution and adrenaline has been reported occasionally.

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 ophthalmic solution should not be used during pregnancy unless clearly necessary. However, if BETOPTIC ophthalmic solution 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 ophthalmic solution 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 ophthalmic solution on human fertility.

4.7 Effects on ability to drive and use machines

BETOPTIC ophthalmic 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

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, dysthymic disorder *Not known*: insomnia, depression
Nervous system disorders	*Common:* headache *Rare*: syncope *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, hypoaesthesia eye, corneal staining, pupils unequal *Not known:* erythema of eyelid
Cardiac disorders	*Uncommon:* bradycardia, tachycardia *Not known:* 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 *Not known:* alopecia
Reproductive system and breast disorders	*Rare*: libido decreased
General disorders and administration site conditions	*Not known:* asthenia

Paediatric population
The safety and IOP-lowering effect of betaxolol 2.5 mg/ml eye drops, suspension has been demonstrated in paediatric patients in a 3-month, multi-centre, double-masked, active-controlled trial. The adverse drug reaction profile of betaxolol 2.5 mg/ml eye drops, suspension was comparable to that seen in adult patients.

4.9 Overdose

An ocular overdose of BETOPTIC ophthalmic solution 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 ophthalmic solution 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-hours reduction in IOP.

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 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 (FEV_1), the Forced Vital Capacity (FVC) and the relation between them (FEV_1/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 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional 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

Benzalkonium chloride, edetate disodium, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Store 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

White opaque plastic DROPTAINER* dispenser containing 5 ml.

6.5 Special precautions for disposal

No special requirements.

Manufactured by:

ALCON-COUVREUR
B-2870 Puurs (Belgium) for Novartis Pharma AG, Basel, Switzerland

* a trademark of Novartis