BETAXOLOL

BETOPTIC*
5 mg /mL (0.5 % w/v)
Sterile Ophthalmic Solution
Beta Adrenoceptor Blocker

1. NAME OF THE MEDICINAL PRODUCT
BETAXOLOL hydrochloride (BETOPTIC*) 5 mg/mL (0.5%) Sterile Ophthalmic Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 mL of BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution contains 5.6 mg betaxolol hydrochloride, equivalent to 5 mg betaxolol
Excipients: disodium edetate, sodium chloride, sodium hydroxide and/or hydrochloric acid for pH adjustment, and purified water.
Preservative: benzalkonium chloride 0.1 mg/mL

3. PHARMACEUTICAL FORM
BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution is formulated as a sterile, multiple-dose solution for topical ophthalmic use. It is clear and colorless solution. It is an isotonic solution, pH 7.4.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution contains betaxolol hydrochloride, a cardioselective beta- adrenergic receptor blocking agent.

BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile 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-antiglaucoma therapy.

4.2. Posology and method of administration
Posology

Use in adults (including elderly), children and adolescents
The usual dose is one drop of BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution in the affected eye(s) twice daily. In some patients, the intraocular pressure lowering response to BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution may require a few weeks to stabilize. Clinical follow up should include a determination of the intraocular pressure during the first month of treatment with BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution. Thereafter, intraocular pressures should be determined on an individual basis at the judgment of the physician. Due to

individual variations in test results, the effect should not be evaluated until after approximately 1 month after treatment.
When a patient is transferred from a single anti-glaucoma agent, continue the agent already used and add one drop of BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution in the affected eye(s) twice a day. On the following day, discontinue the previous anti-glaucoma agent completely and continue with BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile 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. No overall differences in safety or efficacy have been observed between elderly and younger patients.
When a patient is transferred from several concomitantly administered anti-glaucoma agents, individualization is required. Adjustment should involve one agent at a time made at intervals of not less than one week.

Use in hepatic and renal impairment
The safety and efficacy of BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution in patients with hepatic and renal impairment have not been established.

Method of administration
For ocular use.

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 product 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 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 systematically. Due to the beta-adrenergic component in ophthalmic betaxolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agent 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.

  BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile 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.

Hyperthyrodism

- Beta-blockers may also mask the signs of hyperthyroidism.

Muscle Weakness

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

Anaphylactic reactions

- While taking beta-blockers, patients with 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.

Major surgery

- Consideration should be given to the gradual withdrawal of beta-adrenergic 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.

Ocular

- When BETAXOLOL hydrochloride (BETOPTIC*) 5 mg/mL (0.5%) Sterile 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 BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile 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

- BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution contain benzalkonium chloride which may cause irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile 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-adrenergic blocking agents, catecholamine-depleting drugs (such as reserpine), antiarrhythmics (including amiodarone), digitalis glycosides or adrenergic pychotropic drugs.
- There is a potential additive effect on the intraocular pressure when BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution is administered concomitantly with oral beta-adrenergic blocking agents.
- 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 BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution and adrenaline has been reported occasionally.

4.6. Fertility, Pregnancy and Lactation

Fertility

There are no data on the effects of BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution on human fertility.

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.

Betaxolol should not be used during pregnancy unless clearly necessary. However, if BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile 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. BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution can be used during breast-feeding.

4.7. Effects on 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 have been reported during clinical trials with BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution and are classified

according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) or not known (cannot be estimated from the available date). Within each frequency- grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**MedDRA Preferred Term (v. 13.0)**
Psychiatric disorders	*Rare:* anxiety
Nervous system disorders	*Common:* headache *Rare:* syncope
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
Cardiac disorders	*Uncommon:* bradycardia, tachycardia
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
Reproductive system and breast disorders	*Rare:* libido decreased

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

System Organ Classification	**MedDRA Preferred Term (v. 13.0)**
Immune system disorders	hypersensitivity
Psychiatric disorders	insomnia, depression
Nervous system disorders	dizziness
Eye disorders	erythema of eyelid
Cardiac disorders	arrhythmia
Skin and subcutaneous tissue disorders	alopecia
General disorders and administration site conditions	asthenia

4.9. Overdose

A topical overdose of BETAXOLOL hydrochloride (BETOPTIC*) 5 mg/mL (0.5%) Sterile 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 BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution 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, betaxolol reduces elevated as well as normal IOP, whether or not accompanied by glaucoma, and 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 hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution causes local constriction of the ciliary arterioles of rabbits (decreasing after administration during 50 days)

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. Moreover, during therapy with betaxolol, no negative effect on the blood supply to the optic nerve has been observed. Rather, betaxolol maintains or improves ocular blood flow/perfusion.

In three-way masked crossover studies comparing ophthalmic betaxolol to timolol and placebo, BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution 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.

Clinical Safety and Efficacy

BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution has been used successfully in glaucoma patients who have undergone a laser trabeculoplasty and have needed additional long-term hypotensive therapy. BETAXOLOL hydrochloride (BETOPTIC) 5

mg/mL (0.5%) Sterile Ophthalmic Solution has also been well tolerated in glaucoma patients wearing hard or soft contact lenses and in aphakic patients.

BETAXOLOL hydrochloride (BETOPTIC) 5 mg/mL (0.5%) Sterile Ophthalmic Solution 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.

5.2 Pharmacokinetic properties

Betaxolol is highly lipophilic which results in good permeation of the cornea, allowing high intraocular levels of the drug. Plasma exposure to betaxolol is low following topical ocular administration. In clinical pharmacokinetic studies, plasma concentrations were below the quantitation limit of 2 ng/mL.

Betaxolol is characterised by good oral absorption, low first pass loss and a relatively long half-life of approximately 16-22 hours. The elimination of betaxolol is primarily by the renal rather than faecal route. The major metabolic pathways yield two carboxylic acid forms plus unchanged betaxolol in the urine (approximately 16% of the administered dose).

The onset of action of 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.

Absorption

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 and 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 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.

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 Incompatibilities

Not applicable.

6.2 Special precautions for storage

Keep the bottle in the outer carton. Store at temperatures not exceeding 25°C.
Discard 4 weeks after first opening.
Keep out of the sight and reach of children.

6.3 Availability

5 mL white opaque low density polyethylene DROPTAINER* dispenser.

6.4 Special precautions for disposal

No special requirements.

Caution:

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report it to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

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Manufactured by:
ALCON-COUVREUR NV
Rijksweg 14, Puurs, B-2870, Belgium

Marketing Authorization Holder:
NOVARTIS HEALTHCARE PHILS., INC.
Asian Reinsurance Bldg., Salcedo cor. Gamboa Sts.,
Legaspi Village, Makati City