

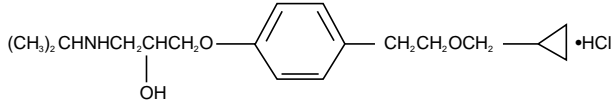
Betoptic S®

(betaxolol HCl)
0.25% as base

S

Sterile Ophthalmic Suspension

DESCRIPTION: BETOPTIC S® Ophthalmic Suspension 0.25% contains betaxolol hydrochloride, a cardioselective beta-adrenergic receptor blocking agent, in a sterile resin suspension formulation. Betaxolol hydrochloride is a white, crystalline powder, with a molecular weight of 343.89. The chemical structure is presented below:



Empirical Formula:

C₁₈H₂₉NO₃•HCl

Chemical Name:

(±)-1-[p-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol hydrochloride.

Each mL of BETOPTIC S Ophthalmic Suspension contains: **Active:** betaxolol HCl 2.8 mg equivalent to 2.5 mg of betaxolol base. **Preservative:** benzalkonium chloride 0.01%. **Inactive:** Mannitol, Poly(Styrene-Divinyl Benzene) sulfonic acid, Carbomer 934P, edetate disodium, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water. DM-00

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

When instilled in the eye, BETOPTIC S Ophthalmic Suspension 0.25% has the action of reducing elevated intraocular pressure, whether or not accompanied by glaucoma. Ophthalmic betaxolol has minimal effect on pulmonary and cardiovascular parameters.

Elevated IOP presents 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. Betaxolol has the action of reducing elevated as well as normal intraocular pressure 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-hour reduction in intraocular pressure.

In controlled, double-masked studies, the magnitude and duration of the ocular hypotensive effect of BETOPTIC S Ophthalmic Suspension 0.25% and BETOPTIC Ophthalmic Solution 0.5% were clinically equivalent. BETOPTIC S Suspension was significantly more comfortable than BETOPTIC Solution.

Ophthalmic betaxolol solution at 1% (one drop in each eye) was compared to placebo in a crossover study challenging nine patients with reactive airway disease. Betaxolol HCl had no significant effect on pulmonary function as measured by FEV₁. Forced Vital Capacity (FVC), 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.

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 and placebo for effects on blood pressure and heart rate.

INDICATIONS AND USAGE: BETOPTIC S Ophthalmic Suspension 0.25% 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.

CONTRAINDICATIONS: Hypersensitivity to any component of this product. BETOPTIC S Ophthalmic Suspension 0.25% is contraindicated in patients with sinus bradycardia, greater than a first degree atrioventricular block, cardiogenic shock, or patients with overt cardiac failure.

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

BETOPTIC S Ophthalmic Suspension 0.25% 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. Treatment with BETOPTIC S Ophthalmic Suspension 0.25% should be discontinued at the first signs of cardiac failure.

PRECAUTIONS:

General:

Diabetes Mellitus. Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrototoxicosis. Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrototoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents, which might precipitate a thyroid storm.

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

Major Surgery. 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.

Pulmonary. 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.

Information for Patients: Do not touch dropper tip to any surface, as this may contaminate the contents. Do not use with contact lenses in eyes.

Drug Interactions: Patients who are receiving a beta-adrenergic blocking agent orally and BETOPTIC S® Ophthalmic Suspension 0.25% should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

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.

Betaxolol is an adrenergic blocking agent; therefore, 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 a history of 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 epinephrine used to treat anaphylactic reactions.

Ocular: 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. When BETOPTIC S Ophthalmic Suspension 0.25% is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Lifetime studies with betaxolol HCl 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 HCl demonstrated no carcinogenic effect. Higher dose levels were not tested.

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

Pregnancy:

Pregnancy Category C. Reproduction, teratology, and peri- and postnatal studies have been conducted with orally administered betaxolol HCl in rats and rabbits. There was evidence of drug related postimplantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was not shown to be teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels. There are no adequate and well-controlled studies in pregnant women. BETOPTIC S should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether betaxolol HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BETOPTIC S Ophthalmic Suspension 0.25% is administered to nursing women.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:

Ocular: In clinical trials, the most frequent event associated with the use of BETOPTIC S Ophthalmic Suspension 0.25% has been transient ocular discomfort. The following other conditions have been reported in small numbers of patients: blurred vision, corneal punctate keratitis, foreign body sensation, photophobia, tearing, itching, dryness of eyes, erythema, inflammation, discharge, ocular pain, decreased visual acuity and crusty lashes.

Additional medical events reported with other formulations of betaxolol include allergic reactions, decreased corneal sensitivity, corneal punctate staining which may appear in dendritic formations, edema and anisocoria.

Systemic: Systemic reactions following administration of BETOPTIC S Ophthalmic Suspension 0.25% or BETOPTIC Ophthalmic Solution 0.5% have been rarely reported. These include:

Cardiovascular: Bradycardia, heart block and congestive failure.

Pulmonary: Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma and respiratory failure.

Central Nervous System: Insomnia, dizziness, vertigo, headaches, depression, lethargy, and increase in signs and symptoms of myasthenia gravis.

Other: Hives, toxic epidermal necrolysis, hair loss, and glossitis. Perversions of taste and smell have been reported.

OVERDOSAGE: 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 S Ophthalmic Suspension 0.25% may be flushed from the eye(s) with warm tap water.

DOSAGE AND ADMINISTRATION: The recommended dose is one to two drops of BETOPTIC S Ophthalmic Suspension 0.25% in the affected eye(s) twice daily. In some patients, the intraocular pressure lowering responses to BETOPTIC S may require a few weeks to stabilize. 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 pilocarpine and other miotics, and/or epinephrine and/or carbonic anhydrase inhibitors can be instituted.

HOW SUPPLIED: BETOPTIC S Ophthalmic Suspension 0.25% is supplied as follows: 2.5, 5, 10 and 15 mL in plastic ophthalmic DROP-TAINER® dispensers.

2.5 mL: NDC 0065-0246-20	10 mL: NDC 0065-0246-10
5 mL: NDC 0065-0246-05	15 mL: NDC 0065-0246-15

STORAGE: Store upright at room temperature. Shake well before using.

Rx Only

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