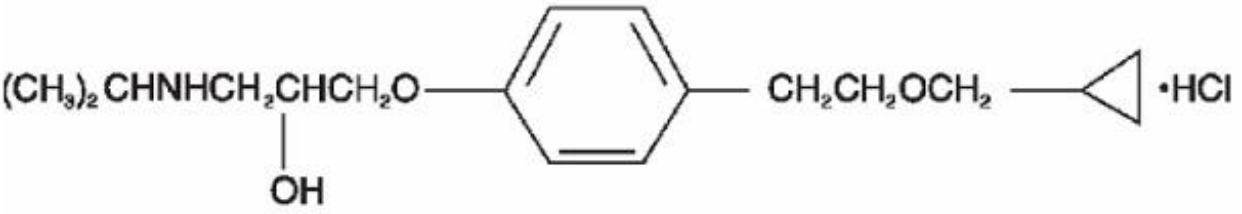
BETOPTIC PILO- betaxolol hydrochloride and pilocarpine hydrochloride
Alcon Laboratories, Inc.

Betoptic®Pilo Ophthalmic Suspension (betaxolol 0.25% / pilocarpine hydrochloride 1.75% ophthalmic suspension)

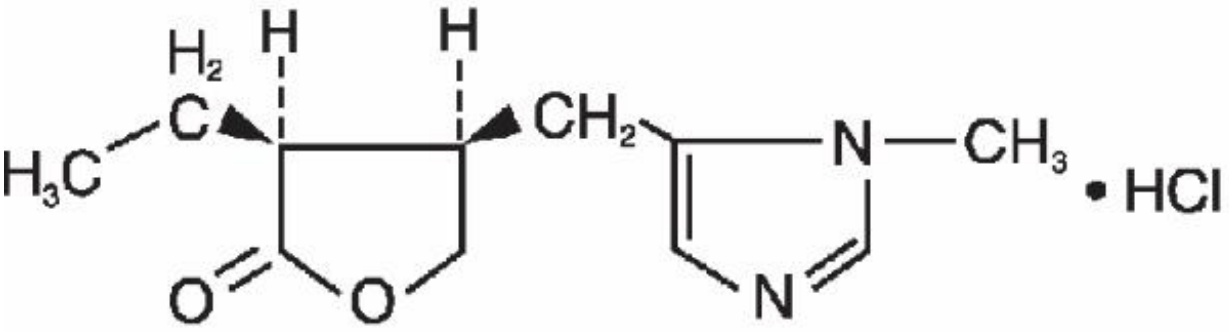
DESCRIPTION

Betoptic®Pilo Ophthalmic Suspension contains betaxolol hydrochloride, a cardiovascular ($beta_1$) adrenoceptor antagonist and pilocarpine hydrochloride, a cholinergic parasympathomimetic agent.

Betaxolol hydrochloride is a white, crystalline powder. Its chemical name is (±)-1[p-(cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol hydrochloride with an empirical formula of $C_{18}H_{29}NO_3HCl$ and a molecular weight of 343.89. The chemical structure of betaxolol hydrochloride is as follows:



Pilocarpine hydrochloride is a white powder. Its chemical name is 2(3H)-furanone, 3-ethyldihydro-4-[(1-methyl-1H-imidazol-5-yl)-methyl]-, monohydrochloride, (3S-cis)- with an empirical formula of $C_{11}H_{16}N_2O_2HCl$ and a molecular weight of 244.72. The chemical structure of pilocarpine hydrochloride is as follows:



Each mL of Betoptic®Pilo Ophthalmic Suspension contains the following:

Active: Betaxolol hydrochloride 2.8 mg equivalent to 2.5 mg betaxolol base and pilocarpine hydrochloride 17.5 mg;

Preservative: Benzalkonium chloride 0.01%.

Inactive: Mannitol, poly(styrene-divinyl benzene) sulfonic acid, carbomer 934P, boric acid, edetate disodium, sodium hydroxide and/or hydrochloric acid to adjust to a pH 6.0-8.0 and purified water.

Betoptic®Pilo Ophthalmic Suspension is provided as a two-part unit for combination by the Pharmacist. It consists of the following components: Part I – a glass syringe containing pilocarpine hydrochloride 8.75%, sodium hydroxide and/or hydrochloric acid (pH 5.0 ± 0.2) and purified water to 1.6 mL; and Part II – a DROP-TAINER® containing betaxolol 0.313%, poly(styrene-divinyl benzene) sulfonic acid, carbomer 934P, boric acid, mannitol, edetate disodium, benzalkonium chloride, sodium hydroxide (pH

8.0 ± 0.2) and purified water to 6.4 mL.

Betoptic® Pilo Ophthalmic Suspension is prepared by affixing a one-inch, blunt, 27 gauge cannula (supplied) to the syringe containing the pilocarpine hydrochloride solution and adding the entire contents of the syringe through the opening in the dropper tip to the DROP-TAINER® containing the betaxolol suspension and mixing well. The final pH of the combination suspension is 6.0 to 8.0

Remove Cap from DropTainer	Add Contents of Syringe through Orifice in DropTainer	Cap and Mix Well. Label with a 2-Week Expiry Period

ADD CONTENTS OF PART I TO PART II AND MIX WELL IMMEDIATELY PRIOR TO DISPENSING AND LABEL WITH A TWO (2) WEEK EXPIRATION DATE

CLINICAL PHARMACOLOGY

Betaxolol hydrochloride, a cardioselective ($beta_1$) adrenoceptor antagonist, 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 subjects 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.

Pilocarpine is a direct acting cholinergic parasympathomimetic agent which acts through direct stimulation of muscarinic neuroreceptors and smooth muscle such as the iris and secretory glands. Each of these compounds lowers elevated intraocular pressure (IOP) by different mechanisms of action. Betaxolol lowers IOP predominately by decreasing aqueous humor production. Pilocarpine lowers IOP predominantly by increasing the outflow of aqueous humor from the eye.

The efficacy and safety of Betoptic® Pilo Ophthalmic Suspension dosed TID was evaluated in two prospective, multicenter, controlled clinical trials. In both controlled studies, Betoptic® Pilo Ophthalmic Suspension dosed TID provide up to an additional 1-3 mmHg IOP lowering from the BETOPTIC®-S BID baseline. Betoptic® Pilo has not been shown to be superior to any other beta-blocker aside from Betoptic®-S.

The potential for systemic absorption was evaluated following topical use of Betoptic® Pilo Ophthalmic Suspension TID. After five and eight days of dosing with Betoptic® Pilo Ophthalmic Suspension TID, plasma levels of betaxolol were below the level of quantification (2.0 ng/mL) indicating that TID dosing results in a low systemic exposure to the drug. Plasma concentrations of pilocarpine were higher following topical ocular administration of Pilocarpine HCl Solution 4% QID than after dosing with Betoptic® Pilo Ophthalmic Suspension TID.

INDICATIONS AND USAGE

Betoptic® Pilo Ophthalmic Suspension is indicated for the reduction of elevated intraocular pressure in patients with primary open-angle glaucoma and ocular hypertension who are insufficiently responsive to Betoptic®-S (failed to achieve target IOP determined after multiple measurements over time).

It is **not** known whether Betoptic® Pilo is equivalent in IOP lowering efficacy to the administration of Betoptic®-S 0.25% and pilocarpine 1.75% dosed separately. It is **not** known whether Betoptic® Pilo is equivalent to other beta-blockers given in combination with pilocarpine.

CONTRAINDICATIONS

Betoptic® Pilo Ophthalmic Suspension is contraindicated in patients with sinus bradycardia, greater than

a first degree atrioventricular heart block, cardiogenic shock or patients with overt cardiac failure.

Betoptic® Pilo Ophthalmic Suspension is also contraindicated in conditions where miosis is undesirable (e.g., peripheral anterior synechia, trauma, acute inflammatory disease of the anterior chamber, glaucoma occurring or persisting after extracapsular cataract extraction when posterior synechia may occur, and papillary block glaucoma).

Hypersensitivity to any component of this product.

WARNINGS

NOT FOR INJECTION OR ORAL ADMINISTRATION. FOR TOPICAL OPHTHALMIC USE ONLY. COMBINE PARTS I AND II PRIOR TO DISPENSING AND LABEL WITH A TWO (2) WEEK EXPIRATION DATE

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.

Betaxolol 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. Betoptic® Pilo Ophthalmic Suspension should be discontinued at the first signs of cardiac failure.

PRECAUTIONS

General

Ocular. Pilocarpine-induced miosis may cause difficulty in dark adaptation. Patients should be advised to exercise caution in night driving and hazardous tasks performed in poor illumination.

In patients with angle-closure glaucoma, the immediate treatment objective is to re-open the angle by constriction of the pupil with a miotic agent. Betoptic® Pilo Ophthalmic Suspension contains pilocarpine HCl 1.75%, a miotic, which, while having an effect on the pupil, is **unlikely** to be sufficient to effectively treat an angle closure event.

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 of acute hypoglycemia.

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

Muscle Weakness. Beta-adrenergic blockage 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 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 such patients with ophthalmic betaxolol have not adversely affected pulmonary function test results, the possibility of adverse pulmonary effects in patients sensitive to beta blockers cannot be ruled out.

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.

Information for Patients

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or disruption of the ocular epithelial surface.

The preservative in Betoptic®Pilo, benzalkonium chloride, may be absorbed by soft contact lenses. Betoptic®Pilo should not be administered while wearing soft contact lenses.

Drug Interactions

Patients who are receiving a beta-adrenergic blocking agent orally and Betoptic®Pilo Ophthalmic Suspension should be observed for a potential additive effect 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 (e.g., reserpine) or calcium-channel blockers because of possible additive effects and the production of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Betaxolol is an adrenergic blocking agent; therefore, caution should be exercised in patients using concomitant adrenergic psychotropic drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies with betaxolol hydrochloride 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 hydrochloride demonstrated no carcinogenic effect. Higher dose levels were not tested. In a variety of *in vitro* bacterial and mammalian cell assays, betaxolol hydrochloride was nonmutagenic.

There have been no long-term studies done using pilocarpine in animals to evaluate carcinogenic potential.

Pregnancy

Teratogenic Effects

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 post-implantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was shown not 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 of betaxolol HCl or pilocarpine in pregnant women. Betoptic®Pilo Ophthalmic Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether topical ocular betaxolol, pilocarpine or Betoptic®Pilo Ophthalmic Suspension is excreted in human milk; however, oral betaxolol is excreted in human milk. Because many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue Betoptic®Pilo Ophthalmic Suspension usage, taking into account the benefit of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

In multi-center controlled clinical trials of Betoptic®Pilo Ophthalmic Suspension the adverse events reported in an approximately 5 to 20% incidence of patients were: headaches, blurred vision, dim vision, abnormal vision, and vitreous disorder.

In the 3-month controlled clinical trials, 12% of patients enrolled on Betoptic®Pilo treatment discontinued the therapy within the first two weeks of treatment because of intolerance due to adverse reactions. In a 24-month long-term safety study, by Month-12, 20% of patients had discontinued and by the Month-24 endpoint, 55% of patients had discontinued Betoptic®Pilo therapy.

The following adverse events were reported at an incidence of 1 to 4% of patients: bronchitis, browache, constipation, dizziness, hyperemia, ocular discomfort, nausea, and pain.

The following adverse events were reported in less than 1% of the patients: abnormal dreams, asthenia, asthma, blepharitis, conjunctival edema, lid erythema, lid margin crusting, lid spasm, palpitation, periorbital edema, photophobia, scotoma, synechiae, and tearing.

In addition, the following adverse events have been associated with ophthalmic formulations containing betaxolol or pilocarpine:

Ocular: Discomfort characterized by burning and stinging upon instillation, ciliary spasm, conjunctival vascular congestion, myopia (especially in younger individuals who have recently started therapy), and reduced visual acuity in poor illumination (frequently experienced by older individuals and individuals with lens opacity), corneal punctate keratitis, itching, dryness of eyes, erythema, inflammation, discharge, ocular pain, decreased visual acuity and crusty lashes. Retinal detachments have been reported with the use of miotics such as pilocarpine and cataracts may occur with prolonged use of pilocarpine.

Additional ocular events reported with other formulations of betaxolol or pilocarpine include allergic reactions, decreased corneal sensitivity, edema, anisocoria, lacrimation, and superficial keratitis (corneal granularity).

Systemic: Cardiovascular; Bradycardia, heart block, and congestive heart failure; Pulmonary; Pulmonary distress characterized by dyspnea, bronchospasm, thickened bronchial secretions, asthma, and respiratory failure; Nervous System; Insomnia, dizziness, vertigo, temporal or supraorbital headaches, depression, lethargy, and increase in signs and symptoms of myasthenia gravis; Other: Hives, toxic epidermal necrolysis, hair loss and glossitis.

Overdosage

No information is available on overdosage of Betoptic®Pilo Ophthalmic Suspension in humans. The symptoms which might be expected with an overdose of a systemically administered beta-1-adrenergic blocking agent are bradycardia, hypotension and acute cardiac failure. Symptoms associated with pilocarpine toxicity include sweating, salivation, gastrointestinal over activity (nausea, vomiting, diarrhea), tremors, bradycardia, hypotension, atrioventricular block, mental status changes, and bronchial constriction (in asthmatic patients).

Dosage and Administration

One or two drops of Betoptic®Pilo Ophthalmic Suspension should be instilled in the affected eye(s) three-times daily.

How Supplied

Betoptic®Pilo Ophthalmic Suspension is supplied as two parts requiring mixing before dispensing. Part I consists of a glass syringe containing pilocarpine hydrochloride sealed in a sterile blister pack also containing a sterile, one inch, blunt, 27 gauge cannula. Part II consists of a DROP-TAINER® containing betaxolol hydrochloride ophthalmic suspension. Once Part I is added into Part II and mixed, the resulting Betoptic®Pilo Ophthalmic Suspension is to be used for no longer than two (2) weeks. At this time, the reconstituted Betoptic®Pilo Ophthalmic Suspension should be replaced.

Storage: Store at 4 – 30°C (40 – 86°F). Shake well before using. Discard reconstituted suspension two (2) weeks after combining.

Caution: Federal (USA) Law Prohibits Dispensing Without a Prescription.

U.S. Patent No's.: 4,252,984; 4,311,708; 4,342,783; and 4,911,920

March 26, 1997

Alcon®

Alcon Laboratories, Inc.

Fort Worth, Texas 76134

BETOPTIC PILO

betaxolol hydrochloride and pilocarpine hydrochloride kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0065-0850

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0065-0850-20	1 in 1 KIT		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1	6.4 mL
Part 2	1	1.6 mL

Part 1 of 2

BETAXOLOL HYDROCHLORIDE

betaxolol hydrochloride suspension

Product Information	
Route of Administration	OPHTHALMIC

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Betaxolol Hydrochloride (UNII: 6X97D2XT0O) (Betaxolol - UNII:O0ZR1R6RZ2)		2.5 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
poly(styrene-divinyl benzene) sulfonic acid ()	
Carbomer 934P ()	
Boric acid (UNII: R57ZHV85D4)	
Mannitol (UNII: 3OWL53L36A)	
Edetate Disodium (UNII: 7FLD91C86K)	
Benzalkonium Chloride ()	
Sodium Hydroxide (UNII: 55X04QC32I)	
Water (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1		6.4 mL in 1 BOTTLE, DROPPER		

Part 2 of 2

PILOCARPINE HYDROCHLORIDE

pilocarpine hydrochloride solution

Product Information	
Route of Administration	OPHTHALMIC

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Pilocarpine Hydrochloride (UNII: 0WW6D218XJ) (Pilocarpine - UNII:01MI4Q9DI3)		17.5 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Sodium Hydroxide (UNII: 55X04QC32I)	
Hydrochloric acid (UNII: QTT17582CB)	
Water (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**

1		1.6 mL in 1 SYRINGE, GLASS		

Labeler - Alcon Laboratories, Inc.

Revised: 6/2006 Alcon Laboratories, Inc.