HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BETAXON™ safely and effectively. See full prescribing information for BETAXON™.

BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5%
Sterile topical ophthalmic drops
Initial U.S. Approval: 1985

----------INDICATIONS AND USAGE----------
BETAXON™ is a beta-adrenergic receptor blocking agent indicated for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension (1).

-------DOSAGE AND ADMINISTRATION--------
- Instill one drop in the affected eye(s) twice daily (2)

-----DOSAGE FORMS AND STRENGTHS---------
- Bottle filled with 5, 10, and 15 mL of 0.5% sterile ophthalmic suspension (3)

----------CONTRAINDICATIONS----------
- Sinus bradycardia, greater than a first degree atrioventricular block, cardiogenic shock, or overt cardiac failure (4).

--------WARNINGS AND PRECAUTIONS---------
- Same adverse reactions found with systemic administration of beta-adrenergic receptor inhibitors may occur with topical ophthalmic administration (5.1)
- Treatment with BETAXON™ should be discontinued at the first signs of cardiac failure (5.2).
- Caution should be exercised in the treatment of glaucoma patients with excessive restriction of pulmonary function. (5.3).
- Beta-adrenergic receptor inhibitors may mask certain clinical signs (e.g. tachycardia) or hyperthyroidism (5.4).

----------ADVERSE REACTIONS----------
Most common adverse reaction is transient ocular discomfort upon instillation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Possible additive ocular and systemic effects in patients receiving oral beta-adrenergic blocking agent (7.1) or catecholamine-depleting drugs (7.2).
- Concomitant adrenergic psychotropic drugs may have additive effects (7.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% is indicated for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose is one drop of BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% in the affected eye(s) twice daily. In some patients, the intraocular pressure lowering responses to BETAXON™ Ophthalmic Suspension may require a few weeks to stabilize. As with any new medication, careful monitoring of patients is advised. The concomitant use of two topical beta-adrenergic agents is not recommended.

3 DOSAGE FORMS AND STRENGTHS

Bottle filled with 5, 10, and 15 mL of 0.5% sterile ophthalmic suspension.

4 CONTRAINDICATIONS

BETAXON™ Ophthalmic Suspension is contraindicated in patients with sinus bradycardia, greater than a first degree atrioventricular block, cardiogenic shock, or patients with overt cardiac failure.

5 WARNINGS AND PRECAUTIONS

5.1 General

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.

5.2 Cardiac Failure

BETAXON™ Ophthalmic Suspension 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 BETAXON™ Ophthalmic Suspension should be discontinued at the first signs of cardiac failure.

5.3 Bronchospasm and Obstructive Pulmonary Disease

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.

5.4 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.

5.5 Muscle Weakness

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

5.6 Surgical Anesthesia

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.

5.7 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.

5.8 Atopy/Anaphylaxis

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.

5.9 Angle-Closure Glaucoma

In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Racemic betaxolol has little or no effect on the pupil. It is expected that levobetaxolol will also have little or no effect on the pupil. When BETAXON™ Ophthalmic Suspension is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Ocular: In clinical trials, the most frequent event associated with the use of BETAXON™ Ophthalmic Suspension 0.5% has been transient ocular discomfort upon instillation (11%). Transient blurred vision has been reported in approximately 2% of patients. Other ocular events have been reported in less than 2% of patients and include: cataracts, and vitreous disorders.

Systemic: Systemic reactions following administration of BETAXON™ Ophthalmic Suspension 0.5% and other topical ocular formations of betaxolol have been at an incidence of less than 2%. These include:

Cardiovascular: Bradycardia, heart block, hypertension, hypotension, tachycardia, and vascular anomaly.
Central Nervous System: Anxiety, dizziness, hypertonia, and vertigo.
Digestive: Constipation and dyspepsia.
Endocrine: Diabetes and hypothyroidism.
Metabolic and Nutritional Disorders: Gout, hypercholesteremia, and hyperlipidemia.
Musculoskeletal: Arthritis and tendonitis.
Pulmonary: Pulmonary distress characterized by bronchitis, dyspnea, pharyngitis, pneumonia, rhinitis, and sinusitis.
Skin and Appendages: Alopecia, dermatitis, and psoriasis.
Special Senses: Ear pain, otitis media, taste perversion, and tinnitus.
Urogenital: Breast abscess and cystitis.
Other: Accidental injury, headache, and infection.

In a three-month, multi-center, double-masked, active-controlled trial in pediatric patients, the adverse event profile of BETAXON™ Ophthalmic Suspension was comparable to that seen in adult and elderly patients.

7 DRUG INTERACTIONS

7.1 Oral Beta-Adrenergic Receptor Blocking Agents

Patients who are receiving a beta-adrenergic

blocking agent orally and BETAXON™ Ophthalmic Suspension should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

7.2 Catecholamine-Depleting Drugs

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.

7.3 Concomitant Adrenergic Psychotropic Drugs

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Reproduction, teratology, and peri- and postnatal studies have been conducted with orally administered betaxolol HCl and levobetaxolol HCl in rats and rabbits. There was evidence of drug related postimplantation loss in rabbits with levobetaxolol HCl at 12 mg/kg/day and sternebrae malformations at 4 mg/kg/day. No other adverse effects on reproduction were noted at subtoxic dose levels.

There are no adequate and well-controlled studies in pregnant women. BETAXON™ Ophthalmic Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether BETAXON™ Ophthalmic Suspension is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BETAXON™ Ophthalmic Suspension is administered to nursing women.

8.4 Pediatric Use

The safety and IOP-lowering effects of BETAXON™ Ophthalmic Suspension have been demonstrated in pediatric patients in a three-month controlled trial.

8.5 Geriatric Use

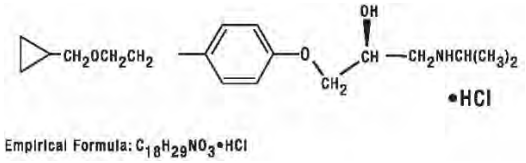
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

11 DESCRIPTION

BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% contains levobetaxolol hydrochloride, a cardioselective beta-adrenergic receptor blocking agent, in a sterile resin suspension formulation. Levobetaxolol hydrochloride is a white, crystalline powder with a molecular weight of 343.89. The specific rotation is:

$[\alpha]_{589nm}^{25°C}$ -19.67° (c=20 mg/mL; methanol)

The chemical structure is:



Empirical Formula: $C_{18}H_{29}NO_3 \bullet HCl$

Chemical Name:
(S)-1-[p-[2-(cyclopropylemethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol hydrochloride.

Each mL of BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% contains: **Active:** levobetaxolol HCl 5.6 mg equivalent to 5.0 mg of levobetaxolol free base. **Preservative:** benzalkonium chloride 0.01%. **Inactives:** mannitol, poly(styrene-divinyl benzene) sulfonic acid, Carbomer 974P, boric acid, N-lauroylsarcosine, edetate disodium, hydrochloric acid or tromethamine (to adjust pH) and purified water. It has a pH of 5.5 to 7.5 and an osmolality

of 260 to 340 mOsm per kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Levobetaxolol is a cardioselective (beta-1-adrenergic) receptor blocking agent that does not have significant membrane-stabilizing (local anesthetic) activity and is devoid of intrinsic sympathomimetic action. Animal studies suggest levobetaxolol (S-isomer) is the more active enantiomer of betaxolol (racemate).

When instilled in the eye, BETAXON™ Ophthalmic Suspension has the action of reducing elevated intraocular pressure. 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.

Since racemic betaxolol and other beta-adrenergic antagonists have been shown to reduce intraocular pressure by a reduction of aqueous production as demonstrated by tonography and aqueous fluorophotometry, it is assumed that the mechanism of action of levobetaxolol is similar.

12.2 Pharmacodynamics

The intraocular pressure lowering effect of racemic betaxolol can generally be noted within 30 minutes and the maximal effect can usually be detected two hours after topical administration. It is assumed that the intraocular pressure lowering time profile of levobetaxolol is similar. A single dose provides approximately a 12-hour reduction in intraocular pressure.

12.3 Pharmacokinetics

BETAXON™ Ophthalmic Suspension 0.5% (levobetaxolol hydrochloride ophthalmic suspension) was dosed topically for 7 days to steady-state in 20 normal volunteers. An average maximal levobetaxolol plasma concentration (C_{max}) of 0.5 ± 0.14 ng/mL was reached about three hours after the last dose. The mean half-life of levobetaxolol was approximately 20 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In lifetime studies in mice at oral doses of 6, 20 and 60 mg/kg/day and in rats at oral doses of 3, 12 and 48 mg/kg/day, betaxolol HCl demonstrated no carcinogenic effect. Levobetaxolol was not mutagenic in the Ames assay, chromosomal aberration, mouse lymphoma, and cell transformation assays *in vitro*. Levobetaxolol demonstrated potential mutagenicity in the sister chromatid exchange assay in Chinese Hamster Ovarian cell *in vitro* in the presence of metabolic activation systems.

14 CLINICAL STUDIES

In two well-controlled clinical studies in which a total of 356 patients were dosed for three months, BETAXON™ Ophthalmic Suspension produced clinically relevant reductions in IOP at a follow-up visit. At 8 AM after nighttime dosing (trough), IOP was reduced from baseline approximately 4 to 5 mmHg (16% to 21%). At 10AM, two hours after dosing (peak), IOP was reduced from baseline approximately 5 to 6 mmHg (20% to 23%).

In comparisons between BETAXON™ Ophthalmic Suspension 0.5% and non-cardioselective beta blockers in reactive airway subjects, BETAXON™ Ophthalmic Suspension is expected to demonstrate less effect on pulmonary function [FEV_1 and Forced Vital Capacity (FVC)].

The cardiovascular effects of BETAXON™ Ophthalmic Suspension 0.5% and betaxolol ophthalmic solution 1% were compared in double-masked, crossover studies to timolol maleate ophthalmic solution 0.5%. Levobetaxolol and betaxolol were shown during exercise to have significantly less effect on heart rate and systolic blood pressure than timolol maleate.

16 HOW SUPPLIED/STORAGE AND HANDLING

BETAXON™ (levobetaxolol hydrochloride ophthalmic suspension) 0.5% is supplied as follows: 5, 10 and 15 mL in a clear LDPE plastic ophthalmic DROP-TAINER® dispenser and a yellow polypropylene screw cap.

5 mL: NDC 0065-0239-05
10 mL: NDC 0065-0239-10
15 mL: NDC 0065-0239-15

STORAGE: Store upright at 39° to 77°F (4° to 25°C).

Protect from Light.
Shake well before using.

17 PATIENT COUNSELING INFORMATION

17.1 Avoiding Contamination of the Product

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

Rx Only
U.S. Patent Nos. 4,911,920; 5,520,920; 5,540,918; 4,342,783; 4,252,984 and Pat. Pending.

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