**BETAGAN®**

Allergan

Levocabonol HCl

Glaucoma Therapy

**Action And Clinical Pharmacology:** Levobunolol is a noncardioselective beta-adrenoceptor antagonist, equipotent at both beta1 and beta2 receptors. Levobunolol is approximately 60 times more potent than the dextro isomer in its beta-blocking activity, yet equipotent in its potential for direct myocardial depression. Accordingly, the levo isomer, levobunolol, is used. Levobunolol does not have significant local anesthetic (membrane-stabilizing) effect or intrinsic sympathomimetic activity.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

Levocabonolol, when instilled into the eye, will lower elevated intraocular pressure (IOP), as well as normal IOP, whether or not accompanied by glaucoma. Elevated IOP is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of optic nerve damage and visual field loss.

The onset of action with 1 drop of levobunolol can be detected within 1 hour after treatment, with maximum effect seen between 2 and 6 hours. A significant decrease in IOP can be maintained for up to 24 hours with once daily dosing of levobunolol 0.5%.

Measurements of aqueous flow and total outflow facility suggest that levobunolol lowers IOP primarily by decreasing aqueous humor production. Levobunolol reduces IOP with little or no effect on pupil size or accommodation, in contrast to the miosis which cholinergic agents are known to produce. The blurred vision and night blindness often associated with miotics would not be expected. This is particularly important in patients with central lens opacities.
who would experience decreased visual acuity with pupillary constriction.

Levobunolol has been shown to be as effective as timolol in lowering intraocular pressure.

In controlled clinical studies of up to 2 years duration, IOP was well controlled in approximately 80% of subjects treated with levobunolol 0.5% b.i.d. The mean IOP decreases from baseline were between 6.87 and 7.81 mm Hg. No significant effects on pupil size, tear production or corneal sensitivity were observed. Topically applied levobunolol at concentrations of 0.5 and 1%, decreased heart rate and blood pressure in some patients. The IOP-lowering effect of levobunolol was well maintained over the course of these studies.

In a 3-month controlled clinical study, once-daily application of levobunolol 0.5% controlled the IOP of 72% of subjects, producing an overall mean decrease in IOP of 7.0 mm Hg. Once-daily application of timolol 0.5% controlled the IOP of 64% of subjects, producing a mean decrease in IOP of 4.5 mm Hg. The difference in overall mean decreases in IOP was statistically significant.

In 2 subsequent 3-month trials comparing levobunolol 0.5% with timolol 0.5% administered once daily, overall differences between the 2 drugs were not significant. A greater percentage of subjects in both the levobunolol groups and the timolol groups maintained adequately lowered intraocular pressure in the latter 2 studies, probably because subjects with severe ocular hypertension, unlikely to be controlled by therapy with a beta-blocker alone, were excluded from the study.

In one 3-month study and one 1-year study, levobunolol 0.25% twice daily controlled the IOP of approximately 63 and 70% of the subjects, respectively. The overall mean decreases from baseline were 5.4 and 5.1 mm Hg respectively.

In another 3-month clinical study, the mean decrease in IOP was significantly greater (more than 2 mm Hg) in the 0.25 and 0.5% levobunolol twice-daily treatment groups than in the betaxolol 0.5% twice-daily treatment group.

The prophylactic effect of topical 0.5% levobunolol HCl on IOP elevations after neodymium: YAG laser posterior capsulotomies was investigated in a controlled study. One drop was administered 30 to 120 minutes prior to the capsulotomy. Eight subjects (38%) in
the vehicle treatment group and none in the levobunolol group experienced increases from baseline in IOP of 10 mm Hg or greater. Mean reductions in IOP from baseline ranged from 2.1 to 2.9 mm Hg in the levobunolol group, while in the vehicle treatment group, IOP increases (4.4 to 6.4 mm Hg) were observed at hours 1, 2, and 3 following capsulotomy.

In a controlled study, 0.5% levobunolol or placebo were administered immediately after a unilateral extracapsular cataract extraction and implantation of a posterior chamber intraocular lens. Treatment continued on a once-daily basis for 7 days. The incidence of IOP elevations from baseline ≥10 mm Hg was 8 subjects (40%) in the vehicle group and 4 subjects (19%) in the levobunolol group. Mean IOP increased from baseline up to 8.6 mm Hg at 24 hours in the vehicle group and up to 2 mm Hg at 24 hours in the levobunolol group.

In another controlled study, levobunolol 0.5% was significantly more effective than betaxolol 0.5% or placebo in preventing increased IOP after cataract extraction and posterior chamber lens placement. Two drops of the assigned medication were administered to the study eye after surgery. A significant mean increase in intraocular pressure from the preoperative to the early postoperative period was noted in the groups treated with betaxolol (6.73 mm Hg), placebo (5.35 mm Hg) and timolol (3.83 mm Hg). Levobunolol-treated eyes showed a mean decrease in pressure of 0.43 mm Hg.

An IOP of 30 mm Hg or greater was found in 3 placebo-treated eyes (15%), 4 betaxolol-treated eyes (20%), 1 timolol-treated eye (5%), and none of the levobunolol-treated eyes. Five placebo-treated eyes (25%), 6 betaxolol-treated eyes (30%), 5 timolol-treated eyes (25%), and 1 levobunolol-treated eye (5%) experienced a pressure rise of 10 mm Hg or greater.

**Indications And Clinical Uses:** The control of intraocular pressure in patients with chronic open-angle glaucoma or mild to moderate ocular hypertension.

**Contra-Indications:** In those individuals with bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease; sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure; cardiogenic shock; or hypersensitivity to any component of this product.
Manufacturers’ Warnings In Clinical States: As with other topically applied ophthalmic drugs, levobunolol may be absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration.

Contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Keep out of reach of children. For external use only. Do not touch dropper tip to any surface, since this may contaminate the solution. Protect from light and excessive heat. Discard any unused solution after end of treatment period.

Precautions: Use with caution in patients with known contraindications to systemic use of beta-adrenoceptor blocking agents. These include abnormally low heart rate and heart block more severe than first degree. Congestive heart failure should be adequately controlled before beginning therapy with levobunolol. In patients with a history of cardiac disease, especially arrhythmia and bradycardia, pulse rates should be monitored.

Use with caution in patients with known hypersensitivity to other beta-adrenoceptor blocking agents.

Use with caution in patients with known diminished pulmonary function.

Lactation: It is not known whether this drug is excreted in human milk. Systemic beta-blockers and topical timolol maleate are known to be excreted in human milk. Caution should be exercised when levobunolol is administered to a nursing woman.

Children: Safety and effectiveness in children have not been established.

Drug Interactions: Levobunolol may have additive effects in patients taking systemic antihypertensive drugs. These possible additive effects may include hypotension, including orthostatic hypotension, bradycardia, dizziness, and/or syncope. Conversely, systemic beta-adrenoceptor blocking agents may potentiate the ocular hypotensive effect of levobunolol.
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 marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

**Adverse Reactions:** Transient burning, stinging or itching, blepharoconjunctivitis and decreases in heart rate and blood pressure have been reported occasionally with the use of levobunolol. Iridocyclitis, headache, transient ataxia, dizziness, lethargy, urticaria and pruritus have been reported rarely. Decreased corneal sensitivity has been noted in a small number of patients. The following additional adverse reactions have been reported with ophthalmic use of beta1 and beta2 (nonselective) adrenergic receptor blocking agents: Body as a whole: headache.

Cardiovascular: arrhythmia, syncope, heart block, cerebral vascular accident, cerebral ischemia, congestive heart failure, palpitation.

Digestive: nausea.

Psychiatric: depression.

Skin: hypersensitivity, including localized and generalized rash.

Respiratory: bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure.

Endocrine: masked symptoms of hypoglycemia in insulin-dependent diabetics.

Special Senses: signs and symptoms of keratitis, blepharoptosis, visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis.

Other reactions associated with the oral use of nonselective adrenergic receptor blocking agents should be considered potential effects with ophthalmic use of these agents.

**Symptoms And Treatment Of Overdose:** Symptoms and Treatment: Overdose has not been reported to date. Should accidental ocular over dosage occur, flush eye(s) with water or normal saline. If accidentally ingested, efforts to decrease further absorption may be appropriate (gastric lavage). The most common signs and symptoms
to be expected with over dosage of a systemic beta-adrenergic blocking agent are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure. Should these symptoms occur, discontinue therapy and initiate appropriate supportive therapy.

**Dosage And Administration:** The recommended starting dose is 1 drop of levobunolol 0.25% twice a day in the affected eye(s). If the clinical response is not adequate, the dosage may be changed to 1 drop of levobunolol 0.5% twice a day in the affected eye(s). Levobunolol 0.5% once a day has been found to be effective in controlling IOP in many patients with mild to moderate open-angle glaucoma and ocular hypertension. As with any new medication, careful monitoring of patients is advised.

Dosages above 1 drop of levobunolol 0.5% twice a day are not generally more effective. If the patient's IOP is not at a satisfactory level on this regimen, concomitant therapy with dipivefrin and/or epinephrine, and/or pilocarpine and other miotics, and/or systemically administered carbonic anhydrase inhibitors, such as acetazolamide, can be instituted.

**Availability And Storage:** 0.25%: Each mL of sterile ophthalmic solution contains: levobunolol HCl 2.5 mg. Nonmedicinal ingredients: benzalkonium chloride 0.004% (as preservative), edetate disodium, polyvinyl alcohol (Liquifilm), potassium phosphate monobasic, sodium chloride, sodium metabisulfite, sodium phosphate dibasic, sodium hydroxide or hydrochloric acid to adjust pH. Plastic dropper bottles of 5, 10 and 15 mL. Protect from light and excessive heat.

0.5%: Each mL of sterile ophthalmic solution contains: levobunolol HCl 5 mg. Nonmedicinal ingredients: benzalkonium chloride 0.004% (as preservative), edetate disodium, polyvinyl alcohol (Liquifilm), potassium phosphate monobasic, sodium chloride, sodium metabisulfite, sodium phosphate dibasic, sodium hydroxide or hydrochloric acid to adjust pH. Plastic dropper bottles of 3 mL (hospitals only), 5, 10 and 15 mL. Protect from light and excessive heat.