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**N19219**

FPL

**Betagan®**  
(levobunolol HCl)  
Liquifilm®  
sterile ophthalmic solution

ALLERGAN PHARMACEUTICALS

DESCRIPTION

BETAGAN (levobunolol HCl) Liquifilm sterile ophthalmic solution is a noncardioselective beta-adrenoceptor blocking agent for ophthalmic use.

**CHEMICAL NAME:** (-)-5-(3-(*tert*-Butylamino)-2-hydroxypropoxy)-3,4-dihydro-1(2*H*)-naphthalenone hydrochloride.

**CONTAINS:**  
levobunolol HCl 0.25%, 0.5%  
with Liquifilm® (polyvinyl alcohol) 1.4%, benzalkonium chloride 0.004%, edetate disodium, sodium metabisulfite, sodium phosphate, dibasic, potassium phosphate, monobasic, sodium chloride, hydrochloric acid or sodium hydroxide to adjust pH, and purified water

**CLINICAL PHARMACOLOGY:** Levobunolol HCl is a noncardioselective beta-adrenoceptor blocking agent, equipotent at both beta<sub>1</sub> and beta<sub>2</sub> receptors. Levobunolol HCl is greater than 60 times more potent than its dextro isomer in its beta<sub>1</sub>-blocking activity, yet equipotent in its potential for direct myocardial depression. Accordingly, the levo isomer, levobunolol HCl, is used. Levobunolol HCl does not have significant local anesthetic (membrane-stabilizing) 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.

BETAGAN (levobunolol HCl) has been shown to be an active agent in lowering elevated as well as normal intraocular pressure (IOP) whether or not accompanied by glaucoma. 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.

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

In a three-month clinical study, a single daily application of BETAGAN 0.5% controlled the IOP of 72% of subjects achieving an overall mean decrease in IOP of 7.0 mm Hg.

In two, separate, controlled studies (one three month and one up to 12 months duration) BETAGAN 0.25% b.i.d. controlled the IOP of approximately 64% and 70% of the subjects. The overall mean decrease from baseline was 5.4 mm Hg and 5.1 mm Hg respectively. In an open-label study BETAGAN 0.25% q.d. controlled the IOP of 72% of the subjects while achieving an overall mean decrease of 5.9 mm Hg.

The onset of action with one drop of BETAGAN can be detected within one 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 following a single dose.

The primary mechanism of the ocular hypotensive action of levobunolol HCl in reducing IOP is most likely a decrease in aqueous humor production. BETAGAN 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 and have not been reported with the use of BETAGAN. This is particularly important in cataract patients with central lens opacities who would experience decreased visual acuity with pupillary constriction.

**INDICATIONS AND USAGE:** BETAGAN 0.25% and 0.5% have been shown to be effective in lowering intraocular pressure and may be used in patients with chronic open-angle glaucoma or ocular hypertension.

**CONTRAINDICATIONS:** BETAGAN is contraindicated in those individuals with bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia, second and third degree atrioventricular block, overt cardiac failure (see WARNINGS); cardiogenic shock; or hypersensitivity to any component of this product.

**WARNINGS:** As with other topically applied ophthalmic drugs, BETAGAN 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 (see CONTRAINDICATIONS).

**Cardiac Failure:** Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

**In Patients Without a History of Cardiac Failure:** Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, BETAGAN should be discontinued.

**Non-allergic Bronchospasm:** In patients with non-allergic bronchospasm or with a history of non-allergic bronchospasm (e.g., chronic bronchitis, emphysema), BETAGAN should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta<sub>2</sub> receptors.

**Major Surgery:** The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. For these reasons, in patients undergoing elective surgery, gradual withdrawal of beta-adrenergic receptor blocking agents may be appropriate.

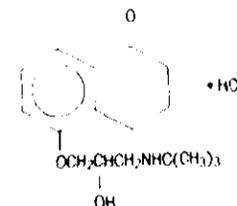
If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol (see OVERDOSAGE).

**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.

**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.

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.

STRUCTURAL FORMULA: levobunolol HCl



## C CAP™ COMPLIANCE CAP Patient Instructions

### INSTRUCTIONS FOR USE *(See reverse also)*

1. On the first usage, make sure the number "1" or the correct day of the week appears in the window. If not, click the cap to the right station.
2. Remove the cap and apply medication.
3. Replace the cap. Hold the C Cap between your thumb and forefinger. Now rotate the bottle until the cap clicks to the next station.
4. When it's time to take your next dose, repeat steps 2 and 3.

**PRECAUTIONS: General:** BETAGAN\* (levobunolol HCl) Liquifilm\* sterile ophthalmic solution should be used with caution in patients with known hypersensitivity to other beta adrenoceptor blocking agents.

Use with caution in patients with known diminished pulmonary function.

In patients with angle closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires, in most cases, constricting the pupil with a miotic. BETAGAN has little or no effect on the pupil. When BETAGAN is used to reduce elevated intraocular pressure in angle closure glaucoma, it should be followed with a miotic and not alone.

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

**Drug Interactions:** BETAGAN should be used with caution in patients who are receiving a beta-adrenergic blocking agent orally because of the potential for additive effects on systemic beta-blockade.

Although BETAGAN used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with BETAGAN and epinephrine may occur.

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 bradycardia and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

**Animal Studies:** No adverse ocular effects were observed in rabbits administered BETAGAN topically in studies lasting one year in concentrations up to 10 times the human dose concentration.

**Carcinogenesis, mutagenesis, impairment of fertility:** In a lifetime oral study in mice, there were statistically significant ( $p \leq 0.05$ ) increases in the incidence of benign leiomyomas in female mice at 200 mg/kg/day (14,000 times the recommended human dose for glaucoma), but not at 12 or 50 mg/kg/day (850 and 3,500 times the human dose). In a two-year oral study of levobunolol HCl in rats, there was a statistically significant ( $p \leq 0.05$ ) increase in the incidence of benign hepatomas in male rats administered 12,800 times the recommended human dose for glaucoma. Similar differences were not observed in rats administered oral doses equivalent to 350 times to 2,000 times the recommended human dose for glaucoma.

Levobunolol did not show evidence of mutagenic activity in a battery of microbiological and mammalian *in vitro* and *in vivo* assays.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 1,800 times the recommended human dose for glaucoma.

**Pregnancy Category C:** Fetotoxicity (as evidenced by a greater number of resorptions) has been observed in rabbits when doses of levobunolol HCl equivalent to 200 and 700 times the recommended dose for the treatment of glaucoma were given. No fetotoxic effects have been observed in similar studies with rats at up to 1,800 times the human dose for glaucoma. Teratogenic studies with levobunolol in rats at doses up to 25 mg/kg/day (1,800 times the recommended human dose for glaucoma) showed no evidence of fetal malformations. There were no adverse effects on postnatal development of offspring. It appears when results from studies using rats and studies with other beta-adrenergic blockers are examined, that the rabbit may be a particularly sensitive species. There are no adequate and well-controlled studies in pregnant women. BETAGAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** 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 BETAGAN is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS:** In clinical trials the use of BETAGAN has been associated with transient ocular burning and stinging in about 1 in 3 patients, and with blepharoconjunctivitis in about 1 in 20 patients. Decreases in heart rate and blood pressure have been reported (see CONTRAINDICATIONS and WARNINGS).

The following adverse effects have been reported rarely with the use of BETAGAN: iridocyclitis, headache, transient ataxia, dizziness, lethargy, urticaria and pruritus.

Decreased corneal sensitivity has been noted in a small number of patients. Although levobunolol has minimal membrane-stabilizing activity, there remains a possibility of decreased corneal sensitivity after prolonged use.

The following additional adverse reactions have been reported with ophthalmic use of beta<sub>1</sub> and beta<sub>2</sub> (non-selective) 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 (see WARNINGS). **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 non-selective adrenergic receptor blocking agents should be considered potential effects with ophthalmic use of these agents.

**OVERDOSAGE:** No data are available regarding overdosage in humans. Should accidental ocular overdosage 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 overdosage with administration of a systemic beta-adrenergic blocking agent are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure. Should these symptoms occur, discontinue BETAGAN therapy and initiate appropriate supportive therapy. The following supportive measures should be considered:

1. Symptomatic bradycardia: Use atropine sulfate intravenously in a dosage of 0.25 mg to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker should be considered.
2. Hypotension: Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or levaterenol. In refractory cases the use of glucagon hydrochloride may be useful.
3. Bronchospasm: Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.
4. Acute cardiac failure: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed, if necessary, by glucagon hydrochloride which may be useful.
5. Heart block (second or third degree): Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

**DOSAGE AND ADMINISTRATION:** The recommended starting dose is one to two drops of BETAGAN 0.5% in the affected eye(s) once a day. Typical dosing with BETAGAN 0.25% is one to two drops twice daily. In patients with more severe or uncontrolled glaucoma, BETAGAN 0.5% can be administered b.i.d. As with any new medication, careful monitoring of patients is advised.

Dosages above one drop of Betagan 0.5% b.i.d. 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.

**HOW SUPPLIED:** BETAGAN\* (levobunolol HCl) Liquifilm\* sterile ophthalmic solution is supplied in white opaque plastic dropper bottles as follows:

Betagan 0.25%:	C Cap™ Compliance Cap B.I.D. (twice daily) 5 mL - NDC 11980-469-25 10 mL - NDC 11980-469-20
Betagan 0.5%: Standard Cap	C CAP™ Compliance Cap Q.D. (once daily) 5 mL - NDC 11980-252-65 10 mL - NDC 11980-252-60 15 mL - NDC 11980-252-61
2 mL - NDC 11980-252-02	C Cap™ Compliance Cap B.I.D. (twice daily) 5 mL - NDC 11980-252-25 10 mL - NDC 11980-252-20 15 mL - NDC 11980-252-21

**NOTE:** Protect from light. Store at controlled room temperature 15°-30°C (59°-86°F).

**CAUTION:** Federal (U.S.A.) law prohibits dispensing without prescription.

Revised June 1989

Allergan America  
1 Formigueros, Puerto Rico 00660

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PR736B 30-6/M

**C CAP™ COMPLIANCE CAP**  
**Patient Instructions**

**IMPORTANT NOTES** *(See reverse also)*

Don't try to catch up on missed doses by applying more than one dose at a time.

Each time you replace the cap, turn it until you hear the click.

The number in the window specifies your next dosage.



Allergan America  
Northridge, CA 91329  
California, U.S.A. Use only  
with aseptic technique.  
For Contents and Usage  
Information, refer to accompanying  
literature.  
Note: Bottle fills to 1.5 capacity  
for proper dose control. Protect  
from light. Store at controlled room  
temperature.

NDC 11980-252-02  
2 mL  
**Betagan**<sup>®</sup>  
(bromobenzol HC1)  
0.5%  
**Liquifilm**<sup>®</sup>  
biphenyl ophthalmic solution  
Allergan **2 mL**

PR 5847 50-74

**ALLERGEN PHARMACEUTICALS**

NSN 6505-01-248-7525

**Contains:**  
le-bunolol HCl, 0.5%  
with: L-glutamine (polyvinyl  
alcohol) 1%, benzalkonium  
chloride (0.004%), edetate  
disodium, sodium phosphate,  
sulfite, sodium phosphate, sal-  
icylic acid, potassium chloride,  
dibasic potassium phosphate,  
monobasic sodium phosphate,  
hydrochloric acid or sodium  
hydroxide to adjust pH, and  
purified water.

**Strength:** Refer to  
package literature.  
**How to Use:**  
Note: Do not dilute to 1:2 ratio.  
Use as directed for proper drop control.  
Protect from light. Store in  
controlled room temperature.

**Allergen America**  
P.O. Box 10000  
Cincinnati, Ohio 45210  
U.S.A.  
See package insert for  
complete prescribing  
information.

NSC 11980-252-25 5 mL  
**Betagan®**  
(betabunolol HCl) 0.5%  
Liquisol™ sterile  
ophthalmic solution with  
**Cap**  
COMPLIANCE CAP  
B.I.O.

PRE584 50-2/M

NSN 6505-01-304-9761

Contains:  
levalbutolol HCl . . . . . 0.5%  
with Liquifilm® (polyvinyl  
alcohol) 1.4%, benzalkonium  
chloride (0.004%), edetate  
sodium, sodium hydroxide,  
hydrochloric acid, potassium  
di-basic, potassium phosphate,  
monobasic, sodium chloride,  
hydrochloric acid or sodium  
hydroxide to adjust pH, and  
purified water.

Dosage: Refer to  
package insert.  
Note: Bottle filled to 1/2 capacity  
for proper drop control.  
Protect from light. Store at  
controlled room temperature.

Allergan America  
Irvine, CA 92618  
Caution: Federal (U.S.)  
patent pending.  
without prescription.

NSC 11289-252-45 5 mL  
**Betagan®**  
(levalbutolol HCl) 0.5%  
Liquifilm® sterile  
ophthalmic solution with  
**C Cap™**  
COMPLIANCE CAP  
**Q.D.**

PR 50055 50-12 M

● ALLERGAN PHARMACEUTICALS

NSN 6505-01-246-6605

Contains:  
levobunolol HCl, 0.5%  
with Liquifilm (polyvinyl alcohol) 1.4%,  
hydroxyethylcellulose (HEC) 0.2%, sodium  
diadum, sodium metasilicate, sodium  
phosphate dibasic, potassium phosphate  
monobasic, sodium chloride, hydrochloric  
acid or sodium hydroxide to adjust pH, and  
purified water.

Caution: Refer to accompanying literature.  
Note: Bottle filled to 2/3 capacity for  
proper drop control. Protect from light.  
Store at controlled room temperature.

Allergan America  
Hormel, Irvine, Puerto Rico 00660  
Caution: Federal (U.S.A.) law prohibits  
dispensing without prescription.

NDC 11980 252 20

10 mL

**Betagan®**  
**(levobunolol**  
**HCl) 0.5%**

Liquifilm® sterile  
ophthalmic solution with

**C Gap™**

COMPLIANCE CAP

**B.I.O.**

PR5862 30-2/M

**Contains:**  
levobunolol HCl ..... 0.5%  
with: Liquifilm® (polyvinyl alcohol) 1.4%  
benzalkonium chloride (0.004%); edetate  
disodium; sodium metabisulfite; sodium  
phosphate, dibasic; potassium phosphate,  
monobasic; sodium chloride; hydrochloric  
acid; sodium hydroxide to adjust pH; and  
buffer salts.

**Dosage:** Refer to accompanying literature.  
**Note:** Bottle filled to 2/3 capacity for  
proper drop control. Protect from light.  
Store at controlled room temperature.

**Allergan America**  
Irvine, California, P.O. Box 00860  
**Caution:** Federal (U.S.A.) law prohibits  
dispensing without prescription.

10 mL  
NDC 11960-252-60  
**Betagan®**  
**(levobunolol  
HCl) 0.5%**  
Liquifilm® sterile  
ophthalmic solution with  
**C Cap™**  
COMPLIANCE CAP  
Q.D.

PR 5910 50-11/7

ALLERGAN PHARMACEUTICALS

Contains:  
betaxolol HCl 0.5%  
with: Lidocaine (polyvinyl alcohol) LAS,  
benzalkonium chloride (0.004%), edetate  
disodium, sodium metabisulfite, sodium  
phosphate dibasic, potassium phosphate,  
monobasic, sodium chloride, hydrochloric  
acid or sodium hydroxide to adjust pH, and  
purified water.

Directions: Refer to accompanying literature.  
Keep: Protect from light.  
Store at controlled room temperature.

Allergan America  
Hormigueros, Puerto Rico 00980  
Cable: "Betad" (U.S.A.); see profile  
or writing without prescription.

15 mL

NSC 1086-252-1  
**Betagan**  
betaxolol  
HCl 0.5%  
Liquiflex® sterile  
ophthalmic solution with  
**C Gap™**  
COMPLIANCE CAP  
B.I.D.

PR 5324 50-87K

● ALLERGAN PHARMACEUTICALS

**Contents:** 0.5% levobunolol HCl with Liofilite® (polyvinyl alcohol), USP, benzalkonium chloride (0.004%), edisate sodium, iso-in-methasone, sodium phosphate dibasic, polysorbate phosphate, sodium hydroxide to adjust pH and purities, water.

**Dosage:** Refer to accompanying literature.

**Notes:** Protect from light. Store at controlled room temperature.

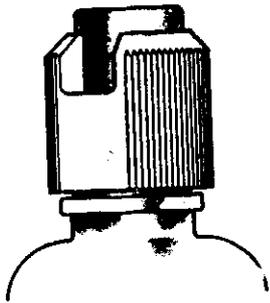
Allergan America  
Hornigwood, Purvis, Faco 0360  
Caution: Federal law prohibits dispensing without a prescription.

15 mL

NDC 11960-252-01  
**Betagan®**  
(levobunolol HCl) 0.5%  
Liofilite® sterile ophthalmic solution with  
**Cooper™**  
COMPLIANCE CAP  
0.0.

PR 5326 50-8/K

15 mL  
ALLERGAN PHARMACEUTICALS



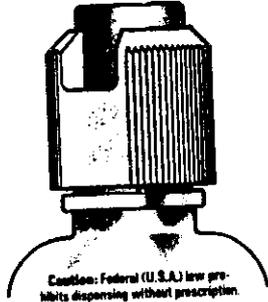
**Betagan®**  
(levobunolol  
HCl) 0.5%  
Liquifilm® sterile  
ophthalmic solution with  
**C Cap™**  
COMPLIANCE CAP  
Q.D.

PR60034 30-0114

hp

15 mL  
ALLERGAN PHARMACEUTICALS

NDC 11980-252-61



Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

**Betagan®**  
(levobunolol  
HCl) 0.5%  
Liquifilm® sterile  
ophthalmic solution with  
**C Cap™**  
COMPLIANCE CAP  
Q.D.

W

105B-08-0190

4

15 mL  
No. 0591  
**Betagan®**  
(levobunolol  
HCl) 0.5%  
with  
**C Cap™**  
COMPLIANCE CAP  
Q.D.

**Contains:**  
levobunolol HCl . . . . . 0.5%  
with: Liquifilm® (polyvinyl  
alcohol) 1.4%; benzalkonium  
chloride (0.004%); edetate diso-  
dium; sodium metabisulfite;  
sodium phosphate, dibasic;  
potassium phosphate, mono-  
basic; sodium chloride; hydro-  
chloric acid or sodium hydroxide  
to adjust pH; and purified water.

**Dosage:** Refer to accompanying  
literature.

**Note:** Protect from light. Store at  
controlled room temperature.

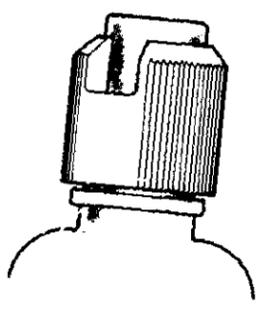


N 3 11980-252-61 8

ALLERGAN PHARMACEUTICALS

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Puerto Rico 00660  
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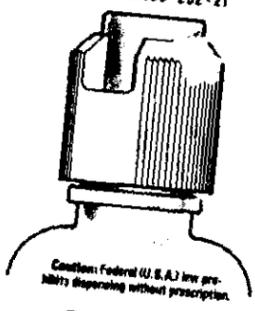
15 mL  
ALLERGAN PHARMACEUTICALS



**Betagan**<sup>®</sup>  
levobunolol  
HCl 0.5%  
Liquifilm<sup>®</sup> sterile  
ophthalmic solution with  
**G Cap**<sup>™</sup>  
COMPLIANCE CAP  
B.I.D.

PR60033 30-8/M

15 mL  
ALLERGAN PHARMACEUTICALS  
NDC 11980-252-21



**Betagan**<sup>®</sup>  
levobunolol  
HCl 0.5%  
Liquifilm<sup>®</sup> sterile  
ophthalmic solution with  
**G Cap**<sup>™</sup>  
COMPLIANCE CAP  
B.I.D.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

LA



COMPLIANCE CAP

levobunolol  
HCl 0.5%

No. 0675

15 mL

**Contains:**  
levobunolol HCl 0.5%  
with: Liquifilm<sup>®</sup> (polyvinyl alcohol) 1.4%; benzalkonium chloride (0.004%); edetate disodium; sodium metabisulfite; sodium phosphate, dibasic; potassium phosphate, monobasic; sodium chloride; hydrochloric acid or sodium hydroxide to adjust pH; and purified water.

**Dosage:** Refer to accompanying literature.

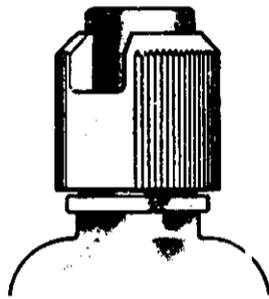
**Note:** Protect from light. Store at controlled room temperature.

ALLERGAN PHARMACEUTICALS

Allergan America  
Formigueros,  
Puerto Rico 00660  
© 1989 Allergan, Inc.

10 mL  
 No. 4927  
 Betagan®  
 (levobunolol  
 HCl) 0.5%  
 with  
 C Cap™  
 COMPLIANCE CAP  
 Q.D.

10 mL  
ALLERGAN PHARMACEUTICALS

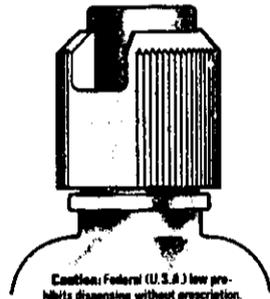


**Betagan®**  
 (levobunolol  
 HCl) 0.5%  
 Liquifilm® sterile  
 ophthalmic solution with  
**C Cap™**  
 COMPLIANCE CAP  
 Q.D.

PR60027 30-8/M

hp

10 mL  
ALLERGAN PHARMACEUTICALS  
NDC 11980 - 252 - 60



Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

**Betagan®**  
 (levobunolol  
 HCl) 0.5%  
 Liquifilm® sterile  
 ophthalmic solution with  
**C Cap™**  
 COMPLIANCE CAP  
 Q.D.

A



106B-07-0190

2

**Contains:**  
 levobunolol HCl ..... 0.5%  
 with: Liquifilm® (polyvinyl  
 alcohol) 1.4%; benzalkonium  
 chloride (0.004%); edetate diso-  
 dium; sodium metabisulfite;  
 sodium phosphate, dibasic;  
 potassium phosphate, mono-  
 basic; sodium chloride; hydro-  
 chloric acid or sodium hydroxide  
 to adjust pH; and purified water.

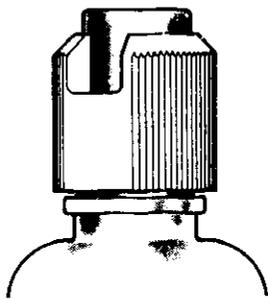
**Dosage:** Refer to accompanying  
 literature.

**Note:** Bottle filled to 2/3 capacity  
 for proper drop control. Protect  
 from light. Store at controlled  
 room temperature.

ALLERGAN PHARMACEUTICALS

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 Hormigueros,  
 Puerto Rico 00960  
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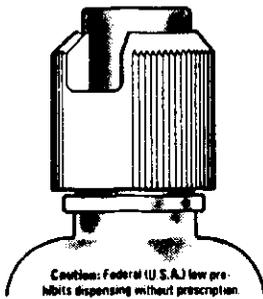
10 mL  
ALLERGAN PHARMACEUTICALS



**Betagan®**  
(levobunolol  
HCl) 0.5%  
Liquifilm™ sterile  
ophthalmic solution with  
**C Cap™**  
COMPLIANCE CAP  
B.I.D.

PR3295 30-2/M

10 mL  
ALLERGAN PHARMACEUTICALS  
NDC 11980-252-20



Caution: Federal (U.S.A.) law pro-  
hibits dispensing without prescription.

**Betagan®**  
(levobunolol  
HCl) 0.5%  
Liquifilm™ sterile  
ophthalmic solution with  
**C Cap™**  
COMPLIANCE CAP  
B.I.D.  
NSN 6505-01-246-6605

P



N 3 11980-252-20 5

COMPLIANCE CAP  
with  
(levobunolol  
HCl) 0.5%  
10 mL  
No. 4926

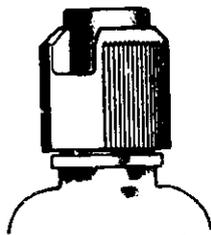
**Contains:**  
levobunolol HCl . . . . . 0.5%  
with Liquifilm® (polyvinyl  
alcohol) 1.4%; benzalkonium  
chloride (0.004%), edetate diso-  
dium, sodium metabisulfite,  
sodium phosphate, dibasic;  
potassium phosphate, mono-  
basic; sodium chloride; hydro-  
chloric acid or sodium hydroxide  
to adjust pH; and purified water

**Dosage:** Refer to accompanying  
literature.

**Note:** Bottle filled to 2/3 capacity  
for proper drop control. Protect  
from light. Store at controlled  
room temperature.

**ALLERGAN PHARMACEUTICALS**  
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Hormigueros,  
Puerto Rico 00660

ALLERGAN PHARMACEUTICALS 5 mL



**Betagan®**  
(levobunolol  
HCl) 0.5%  
Liquifilm® sterile  
ophthalmic solution with  
**G Cap™**  
COMPLIANCE CAP  
Q.D.

PR60026 30-B/M

12

ALLERGAN PHARMACEUTICALS 5 mL  
NDC 11980-252-65



Caution:  
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law prohibits dispensing  
without prescription.  
**Betagan®**  
(levobunolol  
HCl) 0.5%  
Liquifilm® sterile  
ophthalmic solution with  
**G Cap™**  
COMPLIANCE CAP  
Q.D.  
NSN 6505-01-304-9761

M

106C-05-0190

hp

COMPLIANCE CAP  
with  
(levobunolol  
HCl) 0.5%  
No. 4929 5 mL

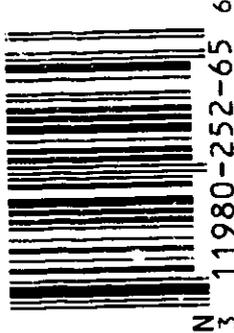
**Contains:**  
levobunolol HCl ..... 0.5%  
with: Liquifilm® (polyvinyl  
alcohol) 1.4%; benzalkonium  
chloride (0.004%); edetate diso-  
dium, sodium metabisulfite,  
sodium phosphate, dibasic;  
potassium phosphate, mono-  
basic; sodium chloride; hydro-  
chloric acid or sodium hydroxide  
to adjust pH, and purified water.

**Dosage:** Refer to accompanying  
literature.

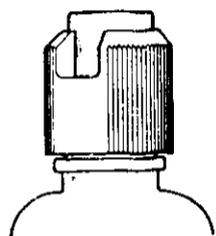
**Note:** Bottle filled to 1/2 capacity  
for proper drop control. Protec-  
from light. Store at controlled  
room temperature.

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ALLERGAN PHARMACEUTICALS 5 mL

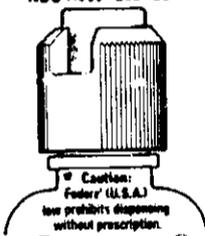


**Betagan®**  
(levobunolol  
HCl) 0.5%  
Liquifilm™ sterile  
ophthalmic solution with  
**C Cap™**  
COMPLIANCE CAP  
B.I.D.

PR3296 30-2/M

ALLERGAN PHARMACEUTICALS 5 mL

NDC 11980-252-25



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Federal (U.S.A.)  
law prohibits dispensing  
without prescription.  
**Betagan®**  
(levobunolol  
HCl) 0.5%  
Liquifilm™ sterile  
ophthalmic solution with  
**C Cap™**  
COMPLIANCE CAP  
B.I.D.  
NSN 6505-01-248-7525



3 11980-252-25 0

K



COMPLIANCE CAP

with  
(levobunolol  
HCl) 0.5%

®  
No. 4928

5 mL

**Contents:**  
levobunolol HCl . . . . . 0.5%  
with: Liquifilm® (polyvinyl  
alcohol) 1.4%; benzalkonium  
chloride (0.004%); edetate diso-  
dium; sodium metabisulfite;  
sodium phosphate, dibasic;  
potassium phosphate, mono-  
basic; sodium chloride; hydro-  
chloric acid or sodium hydroxide  
to adjust pH; and purified water.

**Dosage:** Refer to accompanying  
literature.

**Note:** Bottle filled to 1/2 capacity  
for proper drop control. Protect  
from light. Store at controlled  
room temperature.

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Puerto Rico 00660



PR60040 30-8/M

ALLERGAN PHARMACEUTICALS

NDC 11980-252-02

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

**Betagan**<sup>®</sup>  
(levobunolol HCl)  
0.5%  
**Liquifilm**<sup>®</sup>  
sterile ophthalmic solution

**2mL**

S



N 11980-252-02 1

106C-06-0190

hp

**Betagan**<sup>®</sup>  
(levobunolol HCl)  
0.5%  
**Liquifilm**<sup>®</sup>  
sterile ophthalmic solution

No. 4551

2 mL

**Contains:**

levobunolol HCl ..... 0.5%  
with: Liquifilm<sup>®</sup> (polyvinyl alcohol) 1.4%; benzalkonium chloride (0.004%); edetate disodium; sodium metabisulfite; sodium phosphate, dibasic; potassium phosphate, monobasic; sodium chloride; hydrochloric acid or sodium hydroxide to adjust pH; and purified water.

**Dosage:**  
Refer to accompanying literature.

**Note:**  
Bottle filled to 1/3 capacity for proper drop control. Protect from light. Store at controlled room temperature.

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PHARM

REV

**REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA**

**NDA 19-219 (Original Submission, dated 1/19/84 & Amendment, dated 6/28/84)**

**Date Received: 4/3/84**

**Date Review Completed: 7/24/84 [Waited for additional data (amendment).]**

**Applicant: Allergan Pharmaceuticals, Inc.  
Irvine, CA**

**Drug: BETAGON<sup>®</sup>; ~~Bunolol~~ Bunolol HCl Ophth. Sol'n, 0.25%, 0.5%, 1.0%**

**Code Name: GSH-1355**

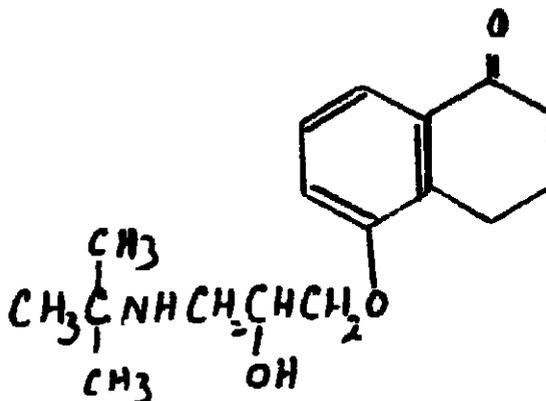
**Category: Beta blocker, topical ophthalmic**

**Formulation: See next page.**

**Related Submissions:**

**Chemistry: Bunolol is a racemic mixture containing equal portions of the "levo" and "dextro" rotatory stereoisomers. Although both isomers have equal ability to cause direct myocardial depression, the "levo" isomer (levobunolol) has more than 60x greater beta-blocking ability than the "dextro" isomer (Kaplan and LaSala, 1970). In order to obtain the highest degree of beta-blocking potential without increasing the potential for direct myocardial depression, the levobunolol isomer was chosen for extensive testing in animal models and humans.**

**Structure:**



1)  
PAGES MISNUMBERED)

NO PAGE 2

OCULAR TOXICITY

Note: For composition of formulations, see table above.

A. One-day Acute Studies in the Rabbit

Animals: 3 F NZ rabbits/group

1. Formulations Tested: 0.2% (6278X) & 2% (6279X) Buno1ol Sol'n

Treatment: One drop (volume not specified) instilled in the lower cul-de-sac of the left eye; the contralateral right eye served as untreated control.

a) 16 Instillations/Day: 1/2 hr. interval between treatments; 2% buno1ol solution; brush-like staining with fluorescein involving 25-50% of the cornea in 1/3 rabbits.

b) 16 Instillations/Day: Because of positive findings, the above experiment was repeated with 2% & 0.2% buno1ol sol'n.

2% Buno1ol Solution: Results with fluorescein staining showed corneal lesions in 3/3 rabbits (2 rabbits with punctate stains, and many closely-packed pinpoint stains in the third rabbit).

0.2% Buno1ol Solution: No ocular reaction.

c) 8 Instillations/Day: 2% Buno1ol sol'n showed no ocular reactions.

2. Formulations Tested: 5% (6616X) buno1ol ophth. sol'n, discard volume, 16 instillations/day. No discomfort; on slit-lamp exam, all 3 rabbits showed slight discharge and moderate conjunctival congestion following the last instillation.

B. Subacute Ocular Toxicity in Rabbits:1. 21-Day Study

Formulation Tested: 1% (6331X) Buno1ol Ophth. Sol'n

Animals: 3 F NZ rabbits/group

Dose Groups:

I	-	1	drop	in	left	eye	2x/day	for	21	consecutive	days
II	-	"	"	"	"	"	8x/day	"	"	"	"
III	-	"	"	"	"	"	16x/day	"	"	"	"

Results: Slit-lamp exam, presumably following fluorescein staining on pretest and on days 7, 14 & 21, showed no ocular reaction in any group.

Histopathology: (HD group only) Veterinary Pathology Consultants, Davis, CA.

Subconjunctival lymphoid nodules in the eyelids; no consistent differences in intensity or distribution between the left and right eyes. The character and distribution of these lymphoid nodules were similar to those seen in normal rabbits under similar conditions. According to the pathologist, "their presence is a reflection of ocular antigenic stimulation and the ability of the individual animal to respond immunologically."

## 2. 28-Day Study in Rabbits

Formulation Tested: 1% (6549X) bunolol ophth. sol'n

Animals: 6 F NZ rabbits/group; 3 groups

### Results:

Low Dose (1 drop 2x/day): No discomfort; slit-lamp and gross exams were negative.

Mid Dose (1 drop 4x/day): Slight discomfort; slit lamp exam (days 7, 14, 21 & 28) showed slight corneal opacity in the untreated right eye; results were otherwise negative. Grossly, there was slight hyperemia in 10/672 instillations in 4/6 rabbits.

High Dose (1 drop 8x/day): There was ocular discomfort at various times in all 6 rabbits.

Slit-lamp exam on days 7, 14, 21 & 28 showed one rabbit with slight conjunctival congestion in both eyes on day 14, and in the untreated eye only on days 21 & 28. One rabbit had slight discharge in the treated eye on day 29. No other ocular reactions were observed.

Gross Exam showed slight hyperemia in 116/134 instillations in all 6 rabbits, slight discharge in 2 instillations in 2 rabbits, and tearing in 97 instillations. One rabbit showed a small closed abscess on the left side of the nose on days 2 & 28. Another rabbit had torticollis (twisted neck).

Note: These 2 animals were identified. Presumably they were: #1277 with plasmocytic meningitis and #1297 with non-suppurative neuritis; Encephalitozoan cuniculi infection [organisms not seen on histopathology (see NDA, page 105064)].

Histopathology: <sup>(HD part only)</sup> (Vet. Pathology Consultants) Corneal limbal lymphoid infiltrate in the treated eye of #1297. Subconjunctival lymphoid nodule occurred randomly in one or both eyes, according to the pathologist, representing immune response to ocular antigenic stimulation. Noted also were randomly-occurring hyperkeratosis and acanthosis of the eye lid.

(Note: No lesions, e.g., vacuoles in the optic nerve.)

**3. 28-Day Study in Rabbits****Formulation Tested:** 5% (6591X) bunolol ophth. sol'n**Methodology:** Same as in the 28-day study with 1% sol'n**Results:** Rabbits from all 3 groups showed some degree of discomfort.

Slit lamp exam on days 7, 14, 21 &amp; 28 showed conjunctival congestion with or without discharge in 6/6 rabbits in the HD &amp; 3/6 in the MD gps.

Grossly, hyperemia and ocular discharge were evidence of local irritation.

**Histopathology:** (HD group only) Vet. Path. Consultants, Inc.Subconjunctival lymphoid nodules randomly distributed and representing immune response to ocular antigenic stimulation. Chronic adenitis of Harder's gland in the right eye of 2 animals was suggestive of infectious process. (Note: No significant lesions in the optic nerve in any rabbit.)**Reviewer's Comment:** Material tested in this study was of higher conc'n (5%) and with a different vehicle than that proposed in the NDA.**4. 28-Day Study****Formulation Tested:** 1% (6617X-6187C) bunolol ophth. sol'n, heat & light stressed**Note:** The test material was the same as proposed for clinical use, but the sol'n had been exposed previously to 45° temperature for 31 days, followed by exposure to 600 footcandles illumination for 15 days.

<u>Criteria</u>	<u>Fresh</u>	<u>Heat &amp; Light Stressed</u>
<u>Concentration:</u>	1.05%	0.890% ± 0.035
<u>pH:</u>	7.1-7.3	5.29 ± 0.07

**Results:****High Dose (1 drop 8x/day):** No ocular discomfort was observed in any rabbit at any instillation. No ocular reactions were observed upon gross observation, or slit-lamp exams done on days 7, 14, 21 & 28.

Low Dose (1 drop 2x/day): No ocular discomfort was observed in any instillation. No ocular reactions were observed upon gross observation. Upon slit-lamp exams (days 7, 14, 21 & 28), +1 conjunctival congestion was exhibited in: both eyes of 1 rabbit and the untreated right eye of another - day 14; the untreated right eye of 1 rabbit - day 21; the treated left eye of 1 rabbit - day 28. No other ocular reactions were observed.

Histopathology: (ND group only; Vet. Path. Consultants, Inc.)

No treatment-related changes in the extraocular tissues; no consistent differences between the treated & untreated eyes.

The pathologist reports:

"Minimal to mild vacuolation of both the right & left optic nerves was seen in 5/6 animals. This change is sporadically seen in the optic nerves of many animal species, and the exact etiological basis is uncertain. In some cases, the change may be artefactual and associated with fixation.

"Subconjunctival lymphoid nodules were common in the lids of both the left & right eyes; these are expected, as they are considered the normal ocular response to antigenic stimulation.

"Generally mild scattered non-suppurative inflammation of the skin was sporadically seen in the left and/or right eyelids. In the present cases, the etiologic basis is unknown. Such mild scattered inflammation is, however, fairly commonly seen in rabbit eyelids."

Reviewer's Comment: The vacuoles in the optic nerve reported in this study were not seen in the 21-day & two other 28-day studies (all reviewed above). Tissues from all these studies were examined by the same pathologist. Furthermore, this lesion was not reportedly seen by another pathologist (Dr. Ackerman, Experimental Pathology Labs) in the eyes exposed to 1-year chronic study with 1% buno101 ophth. sol'n (same formulation, but not heat stressed). In this reviewer's opinion, it is unlikely that heat stress of the formulation was the cause. It appears to be an artefact in the fixation process.

C. Chronic Ocular Toxicity: 1-Year Topical in Rabbits

Animals: 40 F rabbits/group, further subdivided into 4 subgroups (A, B, C, D) of 10 rabbits each. Rabbits in subgroup D were sacrificed at termination (1 year).

Dosage Regimen: All groups were dosed with 1 drop, 2x/day.

<u>Groups:</u>	<u>% Suno101</u>
I. High Dose (HD)	5% (6616X)
II. Mid Dose (MD)	1.0% (6617X)
III. Low Dose (LD)	0.5% (6618X)
IV. Vehicle Control (VC)	0 (6619X)

**Treatment:** One drop of ophth. sol'n was instilled in the left eye b.i.d. (morning & afternoon) daily for 12 consecutive months. Left eyes were dosed and contralateral right eyes remained untreated.

**Termination:** Interim sacrifice at approx. 3 months; terminal sacrifice at 12 months.

**Results:**

**Physical Appearance:** These consisted of diarrhea, earmites, self-inflicted scratches, pinworm, etc. - none related to drug treatment.

**Mortality:** No spontaneous deaths. A total of 10 rabbits (2 MD, 3 MD, 1 LD, 4 VC) were sacrificed prior to their scheduled termination. Six of these had torticollis, 2 were lame (accidental, not neurologic), 1 had otitis media, and 1 MD animal was weak, lethargic & moribund on day 224.

**Gross Ocular Observations:** These were recorded at each instillation. Hyperemia & conjunctival discharge tabulated in the report were recorded at less than 1% of the total observations. Buphthalmos (enlargement of the eye) was observed in 2 rabbits (not identified) of the VC group - in the left eye on day 155 in one rabbit, and in the right eye on day 5 in the other. Both had elevated intraocular pressure (IOP). Moderate corneal opacity was also reportedly observed in the affected eyes. According to the investigators, this was "non-solution related".

**Slit Lamp Exam:** These were performed on days 85, 177, 273 & 352. The Pannus and abnormality of the iris were reportedly not present in any rabbit of treated or control groups. Conjunctival congestion, corneal lesions (recorded as various degrees of cloudiness and fluorescein positive staining - both indicative of corneal opacity) were observed, but their incidence and occurrence was neither dose- nor treatment-related.

**Reviewer's Comment:** All rabbits showing any positive finding on slit lamp exam during the entire study period were followed. According to my tabulation (below), no systematic pattern for the individual animals is apparent.

**One-Year Ocular Toxicity in Rabbits**  
**Slit Lamp Exam**

**Note:** Left eyes were treated; right eyes untreated controls.

	<u>Rabbit No.</u>	<u>Day 85</u>	<u>Day 177</u>	<u>Day 173</u>	<u>Day 352</u>
<b>HIGH DOSE</b>	1609	F1 (L)	-0-	-0-	Not listed.
	1627	F1 (L)	F1 (L)	-0-	CC (L)
	1695	-0-	-0-	Cor (L)	-0-
	1702	-0-	-0-	-0-	CC (R)
	1708	-0-	-0-	CC (L)	-0-
	1709	-0-	-0-	-0-	CC (L)

	<u>Rabbit No.</u>	<u>Day 85</u>	<u>Day 177</u>	<u>Day 173</u>	<u>Day 352</u>
HIGH DOSE (Cont.)	1710	-0-	-0-	CC (R)	-0-
	1741	-0-	CC (R)	-0-	CC (L)
	1746	-0-	-0-	-0-	CC (L)
	1752	CC (L,R)	-0-	-0-	-0-
	1782	-0-	-0-	-0-	CC (L,R)
	1793	-0-	-0-	-0-	CC (L)
	1784	-0-	Cor (L)	-0-	Cor (L)
MID DOSE	1608	-0-	-0-	CC (R)	-0-
	1612	-0-	CC (R)	CC (L)	-0-
	1616	-0-	FI (L)	-0-	-0-
	1617	-0-	FI (L)	-0-	-0-
	1619	CC (L)	-0-	CC (L)	-0-
	1657	Cor (L)	-0-	-0-	-0-
	1692	-0-	CC (L)	-0-	-0-
	1713	-0-	-0-	-0-	CC (R)
	1714	-0-	-0-	-0-	FI (R)
	1716	FI (R)	-0-	-0-	FI (R)
	1749	FI (R)	-0-	-0-	-0-
	1777	CC (R)	-0-	-0-	-0-
LOW DOSE	1633	-0-	Cor (R); FI (R)	-0-	-0-
	1638	-0-	CC (L)	-0-	-0-
	1682	-0-	-0-	-0-	CC (L)
	1684	Cor (L,R); FI (L)	(Sacrificed interim.)		
	1686	Cor (L); FI (L)			
	1725	-0-	-0-	CC (L,R)	-0-
	1727	-0-	-0-	-0-	CC (R)
VEHICLE	1641	-0-	Cor (R)	Cor (R)	Cor (R)
	1646	-0-	Cor (L)	Cor (L)	Cor (L)
	169	CC (R)	-0-	-0-	-0-
	1697	Cor (R)	-0-	Cor (R)	-0-
	1731	-0-	-0-	FI (R)	-0-
	1756	-0-	-0-	-0-	CC (L,R)
	1761	-0-	-0-	-0-	CC (L,R)
	1762	CC (L,R)	-0-	Cor (R)	Cor (R); FI (R)
	1772	-0-	CC (L)	-0-	CC (L); Cor (L)
			Cor (L)	Cor (L)	Flare (L)
	1775	-0-	CC (L,R)	-0-	-0-

Abbreviations: CC = conjunctival congestion (L) = left eye  
 Cor = corneal lesion (R) = right eye  
 FI = fluorescein positive -0- = no abnormality

Ophthalmoscopy: The findings indicative of effects on the lens and the retina of rabbits were as follows:

HD: Small nuclear cataract in treated eye of 1 rabbit, day 352

ND: No abnormalities

LD: Nuclear cataract in 1 rabbit, day 85; another showed an abnormal blood vessel extending into the vitreous humor in the control eye.

VC: One rabbit previously noted to have buphthalmia in the control eye exhibited a small nuclear cataract and congested retinal blood vessel in the control right eye on days 177 & 352, respectively.

Body Wt: No statis. sig. differences between groups.

Hematology & Blood Chemistry: Performed on days, 9, 91, 182 & 357, these were conducted in rabbits from all groups. Sig. levels for various parameters are tabulated in Table 18 (for hematology) and Table 43 (for blood chemistry) of the report (NDA Vol. 1.5, pp. 105195 & 105244). None of the parameters, if statis. sig. different, had any biological importance.

Pathology: (Reported by Experimental Path. Labs, Herndon, VA)

a) Interim Sacrifice on Day 95-96:

- Ocular: Minimal to mild collections of mononuclear cells within the limbal cornea and occurring unilaterally in one eye; its incidence was low and did not appear to be drug-related. Likewise, lymphocytic foci in the nictating membrane occurred unilaterally with low incidence and were not treatment-related. In one rabbit (VC) #1699, lymphocytic foci occurred in both eyes. This rabbit also had non-suppurative perineuritis of the optic nerve in both eyes and non-suppurative meningitis.

- Non-ocular (systemic): Non-specific, mostly in lungs, such as congestion, interstitial pneumonitis & peribronchial lymphocytic hyperplasia; none of these were treatment-related. Submucosal congestion of the trachea was seen in several animals; it was least frequent in the HD and most frequent in the VC group.

b) Final Termination - Day 364/365:

- Ocular: All ocular lesions from all rabbits have been tabulated. Since the tabulations provided in the report were too cumbersome for comparison, the data have been retabulated below:

Ocular Lesions following 1 Year of Topical Administration  
of Bunolol in Rabbits

	High Dose		Mid Dose		Low Dose		Vehicle	
	Right	Left*	Right	Left*	Right	Left*	Right	Left*
<b>Limbal Cornea:</b>								
mononuclear cells	5/29	6/29	10/30	7/30	4/29	6/29	5/29	7/29
heterophils	0	0	0	0	0	1	0	1
<b>Lens: diffuse subcapsular hyalinization</b>	0	0	0	0	0	2	0	0
<b>Cornea: epithelial hyperplasia</b>	0	0	0	0	0	0	0	1
<b>Optic Nerve: perineuritis</b>	0	0	0	0	0	0	1	0
<b>Eyelid:</b>								
mononuclear cells	1	0	3	1	1	0	5	1
lymphoid nodules	2	1	0	0	0	0	0	1
hemorrhagic exudate (surface)	7	6	3	5	3	1	3	1
congestion	0	0	0	0	0	0	1	1
focal blephritis	0	0	0	0	0	0	0	1
<b>Nictating Membrane:</b>								
mononuclear cells	4	6	3	5	2	7	6	1
lymphoid nodules	2	1	0	0	0	0	0	1
congestion	4	2	3	2	2	2	3	1
<b>Lacrimal Gland:</b>								
multifocal dilatation	0	0	0	0	0	1	0	0
mononuclear cells	1	2	3	0	0	2	1	1
multifocal hemorrhage	10	4	10	6	6	8	2	1
nonsuppurative adenitis	2	0	0	1	1	0	1	1
focal nonsup. adenitis	1	2	0	0	1	0	1	0

\*Treated eyes

From the above table, it can be seen that the lesions occurring most frequently were:

1. foci of mononuclear cells in the limbal cornea, eyelid & nictating membrane;
2. lymphoid nodules in the eyelid & nictating membrane;
3. multifocal hemorrhages in the lacrimal gland, ascribed to hemorrhagic exudate on the surface of the eyelids - both necropsy procedure;
4. non-suppurative adenitis of the lacrimal gland;

5. epithelial hyperplasia of the left cornea & perineuritis of the right optic nerve in vehicle controls, both single instances in different animals;
6. two instances of diffuse subcapsular hyalinization of the lens of the left (treated) eye in the LD group.

With the exception of the lesions in the lens (explained below), all ocular lesions were incidental, and were not compound-related.

Non-Ocular (systemic): These involved changes in the lungs of both drug-treated & control rabbits. Subchronic inflammatory changes consisting of minimal to moderate multifocal pneumonitis and perivascular & peribronchial mononuclear cells were present in the individual rabbits in all 4 groups. More acute changes of the lungs consisting of focal or multifocal suppurative pneumonia or focal accumulations of perivascular heterophils were present in an occasional rabbit. None of the inflammatory lung changes were considered by the pathologist to be related to topical admin. of the drug in the left eyes of these rabbits. Other lesions reported (also not treatment-related) were duct ectasia of the mammary gland, lesions due to protozoan disease (Encephalitozoan cuniculi).

Reviewer's Comment: Diffuse subcapsular hyalinization of the lens of the treated eye in 2 LD rabbits (#1638 & 1700) was reported. With the exception of mild corneal congestion of the treated eye of #1638 on day 177, no abnormalities were observed in either animal on slit lamp exam. This lesion reportedly did not occur in any other eye (treated or untreated) in the MD, MD or VC groups. Histopathologist's response to Dr. Kiley (Allergan) was:

"This is in response to your question regarding the evaluation of the lenses from the Terminal Sacrifice Pathology Report on Allergan Study Number 1356-0216-856, One-Year Chronic Eye Toxicity Study in Female Rabbits. Sections of lens from the right and left eyes of each rabbit were evaluated. The microscopic changes were reported under 'Eye, Right' and 'Eye, Left.' The only diagnosis for a specific lens lesion for this study was 'Diffuse Subcapsular Lens Hyalinization' (under right eye and under left eye).

"If you have any additional questions regarding this study, please contact me."

A variety of changes occur in the subcapsular epithelium. The cells proliferate when stimulated by injury or toxic influence (resulting in opacity or anterior subcapsular cataract), and may appear to undergo metaplasia. Later a hyaline membrane is formed between these cells. (See Hogan & Zimmerman's Ophthalmic Pathology, 2nd Ed. pp. 672 & 673).

**OCULAR PHARMACOLOGY****A. Primary Action: Ocular beta-antagonistic activity**

**Methodology:** Since the albino NZ rabbit does not respond to topical beta-adrenoceptor antagonists with an ocular hypotensive response unrelated to systemic cardiovascular effects, the agonist/antagonist model was developed. In this model, ocular hypotensive response to topical 1-epinephrine (beta-adrenocaptor agonist action) is blocked by topical pretreatment with the beta-adrenoceptor antagonist.

A 50 ul drop of various conc'ns of the beta-blockers was administered to a randomly chosen eye in each of 9 rabbits; contralateral eye received saline. One hr later, a 50 ul drop of 0.5% 1-epinephrine HCl (Epifrin) was administered to the same eye receiving the beta-blocker (contralateral eye rec'd saline). IOI<sub>2</sub> was measured at 0, .5, 1, 2, 3, 4, & 6 hrs later.

**Results:** I<sub>50</sub> represents 50% inhibition epinephrine-induced effect in the above-mentioned animal model system. Levobunolol had I<sub>50</sub> =  $1 \times 10^{-4}\%$ . It was slightly less potent than timolol (I<sub>50</sub> =  $7 \times 10^{-5}\%$ ), and approx. 300x more potent than propranolol (I<sub>50</sub> =  $3 \times 10^{-2}\%$ ).

**B. Local Anesthetic Activity**

**Methodology:** Each rabbit was prepared by trimming all lashes & whiskers from areas immediately surrounding the eyes. Prior to the application of ophth. sol'n, a positive response was established. Rabbits then received a 50 ul drop of sol'n in one eye & 0.9% saline in the other. Each eye was tested for anesthesia at 0, 5, 10, 15 & 30 min. by lightly brushing the cornea with the fine tip of an artist's brush (#1 size, 527 delta).

1. Levobunolol (2, 1, & 0.5%) was tested and its action compared with those of proparacaine (Ophthet.c<sup>R</sup>) as 0.5% sol'n & propranolol (2, 1 & 0.5%) - the 2 drugs with a well-established local anesthetic effect. Levobunolol was found to have some local anesthetic effect at all 3 conc'ns, although none was as effective as either proparacaine or propranolol. The most active conc'n (1% rather than 2%) of levobunolol was not as active as the lowest conc'n of propranolol (0.5%). In addition, the onset of anesthesia was not immediate as with proparacaine or propranolol.
2. Dose-response Curve for Bunolol: Peak Activity occurred 5-10 min. following drug instillation and lasted 15-20 min. The ED<sub>50</sub> was 7.8% (3-20%) at 5 min. A comparison with the corneal anesthetic potential of propranolol & proparacaine yielded the following order of potency: proparacaine > propranolol > bunolol. Timolol was inactive as corneal local anesthetic in this assay.

**ABSORPTION, DISTRIBUTION, METABOLISM & EXCRETION**

The following pharmacokinetic studies were conducted by Allergan. In all these studies, buno!ol ophth. sol'n was employed.

**A. Pharmacokinetic Studies Subsequent to Topical Ophthalmic Admin. of <sup>14</sup>C-dl-Bunolol in Rabbits**

**Test Material:** Bunolol ophth. sol'n, 0.5% in vehicle formulation #6619X (same as proposed for marketing); bunolol was labelled at the carbonyl group.

**1. Absorption & Ocular Distribution in Rabbits**

**Methodology:** A 50 ul drop of 0.5% bunolol ophth. sol'n was instilled in the left eyes of 30 F NZ rabbits. The animals were killed at various time intervals and radioactivity (RA) of ocular tissues was measured.

**Results:** T<sub>1/2</sub> (half-life) were:

	Hours
Aqueous humor	1.26
Corneal tissue	1.07
Iris	1.48
Ciliary body	1.63

Max. tissue conc'n in all ocular tissues except conjunctiva & sclera peaked at 30 min.; in conjunctiva & sclera, it peaked at 15 min. Maximum concentrations were:

At	Time	ug/g of Tissue
At 0 minutes:	Corneal tissue	52.09 + 32.21
	Iris	9.66 + 3.73
	Ciliary body	5.18 + 3.37
At 15 minutes:	Sclera	11.97 + 3.11
	Conjunctiva	9.60 + 4.33

Percentage of the total dose found in ocular tissues at various times is tabulated below:

Tissues	Time Intervals					
	15 Min.	30 Min.	60 Min.	180 Min.	240 Min.	360 Min.
	Mean %					
Aqueous Humor	0.22*	0.26	0.22	0.06	0.04	0.01
Choroid/Retina	0.10	0.07	0.03	0.02	0.01	0.007
Ciliary Body	0.06	0.06	0.03	0.01	0.006	0.002
Cornea	1.13	1.28	0.70	0.19	0.08	0.03
Iris	0.06	0.07	0.04	0.01	0.007	0.002
Vitreous Humor	0.01	0.01				
<b>TOTAL</b>	<b>1.60</b>	<b>1.77</b>	<b>1.05</b>	<b>0.31</b>	<b>0.16</b>	<b>0.07</b>

n = 5 except 30 min. time point

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2. Excretion in Urine & Feces following Topical Dosing in Rabbits

50  $\mu$ l of 0.5% bunolol ophth. sol'n was instilled once in the left eye. On days 1, 2, 3, 4, & 5, urine & feces were collected and RA measured.

Average total recovery was 68.19 + 7.19 in the urine and 21.02 + 3.44 in the feces. More than 50% of the RA was excreted in the 24-hr urine; about 10% was found in the 48-hr feces. Total combined excretion was 89% at the end of 5 days, and washing of the cage recovered an additional 3.54% of the original dose.

3. Recovery in Urine & Feces following IV injection in Rabbits

Bunolol was administered at .05mg/kg IV once, and urine & feces were collected at 24, 48, 72 & 96 hrs.

Total recovery was 70.50 + 8.50% in urine and 11.00 + 2.76% in feces.

4. Accumulation following Multiple Topical Dosing in Rabbits

In a total of 24 rabbits, 50  $\mu$ l of 0.5% bunolol ophth. sol'n was instilled twice daily in both eyes for 4 consecutive days. Ocular tissues (3 rabbits/sampling time) were sampled daily, immediately prior to (for trough level) and 30 min. following the second daily dose (for peak level).

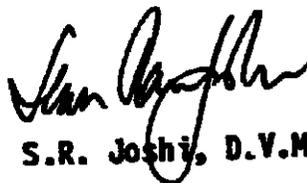
Results showed that there was no sig. accumulation of the drug in the ocular tissue.

COMMENTS & RECOMMENDATIONS

1. Bunolol is a beta-adrenergic blocking agent. It exists as a racemic mixture of levo- and dextro-stereoisomers. The separated levo-isomer, levobunolol (the subject of this NDA) is claimed to have 60x greater beta-blocking activity.
2. The preclinical animal data in this NDA include results of both ophthalmic and systemic studies.
3. I have reviewed the preclinical ophthalmic data and have provided comments

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5. The fact that the lenticular lesion did not occur in any rabbits in the mid-dose, high-dose or vehicle control groups makes interpretation somewhat difficult. The Medical Officer is requested to provide his input in this matter.
6. On the basis of the ophthalmic data, I see no objection from the safety standpoint to approval of this NDA. The Division of Cardiorenal Drug Products (HFN-110) should be consulted for an assessment of safety based on the preclinical systemic data, which I presume they have reviewed.



S.R. Joshi, D.V.M., Ph.D.

cc: Orig. NDA

~~HFN-815~~

HFN-815/MO

CSO

HFN-220

HFN-815/SRJoshi/smc/8/31/84

R/d init.by: JMDavitt

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MED

REV

**Medical Officer's Review of NDA 19-219**

**January 24, 1985**

**Sponsor:** Allergan  
2525 Dupont Drive  
Irvine, CA 92713

**Name of Drug:** Trade: Betagan Liquifilm Sterile Ophthalmic Solution  
Generic: Levobunolol hydrochloride

**Pharmacologic Category:** Beta-adrenergic blocking agent

**Proposed Indication:** Anti-glaucoma

**Dosage Form and Route of Administration:** 0.25%, 0.5%, and 1.0% ophthalmic solution for topical application to the eye twice daily.

**Related Drugs:** Timolol Maleate (TIMOPTIC) NDA 18-086

**Pharmacology:** Levobunolol is a non-selective B-adrenergic blocking agent with actions similar to propranolol, nadolol, timolol and metoprolol. These compounds have been used in the management of hypertension, the prophylaxis of angina pectoris and the control of certain types of cardiac arrhythmias. Timolol maleate (TIMOPTIC) is the only one currently approved for the treatment of chronic glaucoma.

Bunolol is a racemic mixture containing equal portions of the "levo" and "dextro" rotating stereoisomers. Although both isomers have equal ability to cause direct myocardial depression, the "levo" isomer (levobunolol) has more than 60 times greater beta-blocking activity than the "dextro" isomer. In order to obtain the highest degree of beta blocking potential without increasing the potential for direct myocardial depression, the levobunolol isomer was chosen for testing in animal models and humans.

The ocular beta-adrenergic blocking properties of various compounds were assessed in rabbits by determining the topical concentration of the test drug necessary to block the hypotensive effect of topical 0.5% epinephrine. Levobunolol was less potent than timolol, but approximately 300 times more potent than propranolol.

Topically applied levobunolol (0.3% - 10%) was tested for its acute corneal local anesthetic activity in rabbits. Peak activity occurred at 5-10 minutes following drug instillation and lasted 15-20 minutes. The average concentration producing 50% of maximum effect was 7.8% five minutes after dosing. Levobunolol was approximately one-tenth as potent as propranolol and one-hundredth as potent as proparacaine. In long-term studies, levobunolol 0.5%, 1.0% and 3% were administered topically to groups of rabbits twice daily for one year. Corneal anesthetic effects of levobunolol were assessed

following the last daily dose. Peak activity occurred 5 to 10 minutes post-instillation and lasted 15-20 minutes. Full corneal sensitivity returned within 30 minutes, suggesting that there is no cumulative effect of chronic application of levobunolol to the eye.

Ocular absorption and distribution were also studied utilizing C-14 labeled drug. Radioactivity appeared rapidly in various ocular tissues, with peak values after 15 minutes in the scleral and conjunctival tissues and at 30 minutes in other ocular tissues. Corneal concentrations were higher than those in other external tissues. The iris had higher concentrations than other internal tissues.

The ocular effect in rabbits of 1% levobunolol solution was evaluated following 21 and 28 consecutive days of multiple topical instillations (1 drop 2x/day, 1 drop 4x/day and 1 drop 8x/day); the drug was found to be nontoxic in all dosage groups. Signs of slight discomfort and slight hyperemia were noted at a few instillations in the mid-dose and high-dose groups. One animal in the high-dose group showed a slight discharge in the treated eye upon slit lamp examinations on the last day of the study, and another animal showed slight conjunctival congestion in both eyes at one slit lamp examination. Histological examinations showed no changes to ocular tissues attributable to the test solution.

Chronic toxicity studies with 0.5%, 1.0% and 5.0% levobunolol ophthalmic solutions were conducted in rabbits that had received one drop twice daily in the left eye with the right eye serving as a control. Histopathologic examination of tissues was completed after one year of treatment and there were no apparent ocular or systemic solution-related effects.

Clinical Background: Levobunolol has been studied in several other countries including Canada and Germany where it is in the final stages of approval for marketing.

Literature References:

Duzman E, Ober M, Scharrer A, Leopold I. A Clinical Evaluation of the Effects of Topically Applied Levobunolol and Timolol on Increased Intraocular Pressure. *Amer J Ophthalmol* 94:318-27, 1982.

The authors performed a short-term (24 hours) double-masked study on 16 subjects. They noted the onset of effect of a single drop of 0.5% levobunolol to occur within the first hours, with a maximal hypotensive effect of more than 8 mm Hg occurring after two hours. An intraocular pressure decrease of more than 9 mm Hg persisted during a trial in which the patients were treated twice daily. Systemic effects of both drugs (Timolol 0.5% and levobunolol 0.5% and 1.0%) included a consensual intraocular pressure decreasing effect in the untreated eye and clinically significant reductions in heart rate. Diastolic blood pressure was also noted to be decreased at two and four hours after administration of 0.5% levobunolol.

**Fertman LG, Kass HA, Gordon M. A Dose-Response Study of the Effect of Levobunolol on Ocular Hypertension.**

The authors conducted a one day randomized, double-masked, placebo-controlled, dose-response study on levobunolol 0.3%, 0.6%, 1% and 2% in 48 patients with ocular hypertension. The 0.3% and 0.6% concentrations decreased intraocular pressure significantly from baseline levels up to four hours, whereas the 1% and 2% concentrations significantly decreased the pressure up to 12 hours. No objective or subjective side effects were noted.

**Related NDA:** Timolol Maleate (NDA 18-086), also a non-selective beta adrenergic blocking agent, was approved for marketing in the U.S. in 1978. It has become the drug of choice in most cases of glaucoma, but is contraindicated in patients with asthma and other cardiopulmonary problems. The labeling for timolol specifically advises against its use in patients with bronchial asthma and severe chronic obstructive pulmonary disease, and warns that "severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely deaths in association with cardiac failure, have been reported following administration of TIMOPTIC." Documentations of the respiratory adverse reactions is found in the published literature including the FDA Drug Bulletin dated 11/81, and in the National Registry of Ocular Side Effects. Levobunolol, the subject of this review, is not expected to have any cardiopulmonary safety advantage over timolol.

### Clinical Studies

#### I. Single drop, dose finding studies

##### A. Protocol No. LBUN-101-6617 (Michael Kass, M.D.)

**Objective:** To evaluate the dose-response to single-drop instillations of levobunolol ophthalmic solution (in concentrations of 0.03%, 0.3%, 0.6%, 1.0% and 2.0%) with respect to: 1) the onset, magnitude and duration of ocular hypotensive efficacy in subjects with open-angle glaucoma or ocular hypertension; 2) ocular and systemic safety.

**Number of Subjects:** 49

**Type of Study:** Single-dose, randomized, placebo-controlled, and double-masked. Eight subjects were included in each treatment group except for the 0.3% group which was composed of nine subjects. Four subjects were eventually excluded from analysis.

#### Results:

1. 0.03% levobunolol produced significant decreases in IOP at hours 4, 6, and 16 only.
2. 0.3% and 0.6% levobunolol produced significant decreases in IOP at all times except hours 6 and 24 for the 0.6% and hour 24 for 0.3%.

3. 1.0% levobunolol produced significant decreases in IOP at all evaluations including 24 hours.
4. The 1.0% levobunolol group was not significantly different from the 2.0% group.
5. 0.6%, 1.0%, and 2.0% produced absolute pressure reductions greater than 10 mm Hg at 2 hours.
6. Visual acuity and pupil size were not affected by any strength of levobunolol.
7. Anterior chamber flare (increased protein content) was noted in 12 subjects in an apparently dose-related manner, except that none of the 2.0% group had this finding. The significance of this is unclear.
8. Minor subjective complaints were reported by five subjects.
9. Heart rates were significantly decreased from baseline at 2 hours in the 1.0% group and at 1 and 2 hours in the 2.0% group.
10. A significant decrease in systolic blood pressure (average 10 mm Hg) occurred only in the 2.0% levobunolol group. Diastolic blood pressure was only minimally affected by any strength of the drug.

Adverse Reactions: None reported.

- General Conclusions: 0.6% and 1.0% levobunolol produce significant reductions in intraocular pressure in subjects with glaucoma or intraocular hypertension for up to 16 hours (0.6%) and 24 hours (1.0%). Significant change in blood pressure (systolic and diastolic) do not occur with drug concentrations of less than 2.0%, but heart rate is significantly reduced by 1.0% levobunolol.

- B. Protocol No. LBUN-102-6617 (Irving H. Leopold, M.D.)

Objective: To evaluate the dose-response to single drop instillations of levobunolol ophthalmic solution (in concentrations ranging from 0.03% to 2.0%).

Study Population: 12 normal subjects

Study Treatments: Five concentrations of levobunolol (0.03%, 0.3%, 0.6%, 1.0% and 2.0%) and placebo.

**Results:** The ocular effect of levobunolol was observed within one hour and 24 hours, with the maximal effect 2 to 6 hours after instillation. The 0.3% levobunolol group displayed significant decreases in IOP at all evaluations except hour 6. The 0.6%, 1.0% and 2.0% concentrations displayed significant decreases in IOP at all evaluations.

## II. Short Term Safety, Efficacy and Dose-Titration Studies

### A. Protocol No. LBUN-103-6617 (E. Keates, M.D. and R. Bensinger, M.D.)

**Objective:** To evaluate the ocular hypotensive efficacy and the ocular and systemic safety of 0.5% and 1.0% levobunolol ophthalmic solution administered twice daily.

**Number and Type of Subjects:** Forty-six volunteers with chronic open-angle glaucoma or ocular hypertension (16 on 0.5% and 14 on 1.0% levobunolol and 16 on placebo).

**Type of Study:** Three months, randomized, double-masked, and placebo-controlled. Following a washout period, medications were instilled b.i.d. in both eyes. Efficacy was assessed by evaluating changes from baseline in IOP, cup-disc ratios, and visual fields. Ocular safety was assessed by evaluating changes from baseline in visual acuity, pupil size, corneal sensitivity, Schirmer tear test values, and biomicroscopic and ophthalmoscopic findings. Systemic safety was assessed by evaluation heart rate, blood pressure, ECG, laboratory blood analysis, and auscultation of the heart.

### Results

1. At all follow-up visits, mean reductions in IOP from baseline ranged between 7.15 to 11.27 mm Hg for both 0.5% and 1.0% levobunolol treatment groups, whereas, changes in IOP in the placebo-treatment group were minimal.
2. Forty percent of the placebo-group was terminated for inadequate control of IOP, while only 8% of the 1.0% and 14% of the 0.5% levobunolol groups were terminated for this reason.
3. A few changes were seen in visual acuity, pupil size, corneal sensitivity and slit lamp and ophthalmoscopic findings, that were minimal and similarly distributed between drug and placebo treated groups. These changes were felt to be within the range of normal variation routinely observed in subjects with glaucoma.
4. No change in visual fields occurred during the study.

5. Four subjects (3 on 0.5% and 1 on 1.0% levobunolol) had measured heart rates of less than 55 beats per minute at one or more follow-up visits.
6. An average decrease in systolic blood pressure of 4.90 to 5.72 mm Hg occurred in all three groups. However, 12 subjects showed decreases in systolic blood pressure of 20 mm Hg or greater at one visit and 3 subjects on 1.0% levobunolol showed such decreases at more than two visits.

Clinically significant decreases in diastolic blood pressure (>10 mm Hg) were observed in a total of 3 subjects in the placebo group, 6 subjects in the 0.5% and 11 subjects in the 1.0% levobunolol group.

7. Stinging and burning occurred in 2 of the 16 subjects on 0.5% levobunolol and in 5 of the 14 subjects on 1.0% levobunolol.

Adverse Reactions: None reported.

Conclusions: 92% of patients on 1.0% and 86% of patients on 0.5% levobunolol had intraocular pressure reductions compatible with satisfactory control of glaucoma in the opinion of the investigators.

- B. Protocol No. LBUN-104-6617 (T. Zimmerman, M.D., D. Long, M.D., G. Spaeth, M.D.)

Objectives:

1. To determine by titration the effective dose of topically applied levobunolol for controlling IOP in subjects with open-angle glaucoma.
2. To compare the safety of topically applied levobunolol with timolol in subjects with glaucoma or intraocular hypertension.

Study Population: 56 subjects with glaucoma or ocular hypertension.

Study Medications:

1. 0.25%, 0.5%, and 1.0% levobunolol
2. 0.125%, 0.25%, and 0.5% timolol

**Methods:** The study was a parallel, double-masked dose titration clinical trial with random assignment of subjects to either the levobunolol or timolol treatment groups. All variables were evaluated at baseline and frequently over the three month follow-up period on the lowest dose of medication that adequately controlled IOP. If IOP was uncontrolled, treatment was increased to the intermediate dose, and, if still uncontrolled during the three month period on that dose, the treatment was increased to the highest dose.

**Results:**

1. Fifteen of 24 (65%) were adequately controlled for three months on 0.25% levobunolol.
  2. An additional 13% of the subjects were adequately controlled on the intermediate and highest concentrations tested.
  3. Mean IOP decreases ranged from 5.5 to 8.3 mm Hg in both groups with the lowest concentrations.
  4. Fifty-two percent in the levobunolol treated subjects and 31% of the timolol group showed clinically significant decreases in heart rate ( $> 15\%$ ) at one or more follow-up visits.
  5. Observed changes in visual acuity, pupil size, biomicroscopic and ophthalmoscopic findings were within the range of normal variation routinely observed in glaucoma subjects.
  6. The effect of levobunolol on blood pressure in all treatment groups in this study was minimal and of limited clinical significance.
- C. Protocol No. LBUN-110-6677 (A. Charap, Ph.D., M.D., R. Starper, M.D. T. Mandel, M.D.)

**Objective:** To evaluate the ocular hypotensive efficacy and ocular and systemic safety of 0.5% and 1.0% levobunolol q.d. compared with 0.5% timolol, q.d. in subjects with open-angle glaucoma or ocular hypertension.

**Results:** The study was incomplete at the time this NDA was filed. In 59 subjects being followed, mean reductions in IOP from baseline ranged from 4.5 to 9.3 mm Hg at all follow-up visits for all three treatment groups. No adverse effects have been reported.

**III. Long-Term Safety and Efficacy Studies.**

- A. Protocol No. LBU-105-6617 (H. Cohen, M.D., D. Epstein, M.D., R. Forster, M.D., Lass, M.D.)

**Objective:** To evaluate the long-term ocular hypotensive efficacy and the ocular and systemic safety of 0.5% and 1.0% levobunolol ophthalmic solutions b.i.d. compared with 0.5% timolol b.i.d. in a double-masked study in subjects with chronic open-angle glaucoma or ocular hypertension.

**Study Population:**

1. One-hundred-forty-four subjects with ocular hypertension or chronic open-angle glaucoma were entered into the study. (48 on 0.5% levobunolol, 51 on 1.0% levobunolol and 45 on 0.5% timolol).
2. Forty-one subjects were disqualified:
  - a. Eight for drug un-related reasons.
  - b. Twenty-two for inadequate control IOP (seven on 0.5% timolol, seven on 0.5% levobunolol and eight on 1.0% levobunolol and 3 on 1.0% levobunolol).
  - c. Eight for adverse experiences (two on 0.5% timolol, three on 1.0% levobunolol).
  - d. Three for addition of a non-qualifying drug during the study.

**Study Methods:** The study was a parallel, double-masked clinical trial with random assignment of subjects to treatment groups. Following a washout interval, medications were instilled twice daily in both eyes. All variables were evaluated at baseline and frequently over a fifteen-month follow-up period.

**Efficacy Results:**

1. At all follow-up visits, mean reductions in IOP ranged between 6.3 and 8.4 mm Hg in all three treatment groups, with an overall mean IOP reduction of 7.55 mm Hg for 0.5% timolol, 6.8 mm Hg for 0.5% levobunolol, and 6.9 mm Hg for 1.0% levobunolol (Table 1).

Table 1

**Intraocular Pressure (mm Hg): Change from Baseline  
Conventional Analysis**

Day	<u>0.5% Timolol</u>			<u>0.5% Levobunolol</u>			<u>1.0% Levobunolol</u>			<u>Among-group p-values*</u>
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
1 (baseline)	42	27.01	3.19	48	26.32	2.94	51	25.96	2.63	NS
4	38	-7.29**	2.91	39	-6.79	2.87	43	-7.40	3.21	NS
8	33	-7.91	3.05	42	-7.15	2.49	38	-6.92	2.96	NS
15	39	-7.64	2.44	45	-6.73	3.40	44	-7.33	2.99	NS
29	32	-7.75	3.29	35	-7.00	2.73	38	-7.08	3.01	NS
43	34	-8.06	3.15	36	-6.90	2.66	39	-7.22	3.08	NS
57	33	-8.11	3.24	37	-6.30	2.56	36	-7.35	2.72	0.015
85	29	-7.16	3.35	31	-6.82	2.69	32	-6.98	2.84	NS
113	32	-7.17	2.98	39	-7.15	2.09	34	-6.88	2.91	NS
169	27	-7.76	3.31	33	-6.80	2.58	29	-6.95	2.93	NS
260	19	-7.84	3.57	19	-7.68	2.84	25	-7.02	2.64	NS
337	18	-7.28	2.66	16	-7.28	2.55	12	-8.08	2.8	NS
435	9	-8.33	4.09	9	-6.67	3.14	4	-7.38	1.80	-
<b>OVERALL MEAN</b>		<b>-7.55</b>			<b>-6.81</b>			<b>-6.90</b>		<b>NS</b>

\* When between-group comparisons were made on Day 57, mean decreases in the 0.5% timolol group were significantly greater than the 0.5% levobunolol group.

\*\* All groups showed significant changes from baseline at each follow-up day ( $p < 0.001$ ).

NS = Not Significant

Safety Results:

1. Clinically significant decreases ( $> 15\%$ ) in heart rate occurred in several subjects as follows:
  - a. Four in the 0.5% timolol group.
  - b. Eight in the 0.5% levobunolol group.
  - c. Ten in the 1.0% levobunolol group.
2. Systolic blood pressure:
  - a. Mean changes from baseline were not different among the groups.

- b. Clinically significant decreases ( $> 20$  mm Hg) occurred as follows:
1. Fifteen 0.5% timolol subjects had a total of 59 events.
  2. Ten 0.5% levobunolol subjects had a total of 26 events.
  3. Fourteen 1.0% levobunolol subjects had a total of 30 events.
3. Diastolic blood pressure: Clinically significant decreases ( $> 10$  mm Hg) occurred as follows:
- a. Twenty-two 0.5% timolol subjects had a total of 66 events.
  - b. Twenty-eight 0.5% levobunolol subjects had a total of 73 events.
  - c. Twenty-nine 1.0% levobunolol subjects had a total of 98 events.
4. The most common subjective complaints were "burning, stinging and irritation". These were evenly distributed among all groups.

**Conclusion:** This study demonstrates that during 15 months of treatment, levobunolol produces an ocular hypotensive response of similar efficacy and safety to timolol. Additionally, the mean response of 0.5% levobunolol is not statistically different from that of 1.0% levobunolol. Non-life threatening adverse experiences occurred with similar frequency in all three test groups (approximately 5%).

- B. Protocol No. LBUN-106-6617 (A. Cinotti, M.D., D. Cinotti, M.D., W. Grant, M.D., I. Jacobs, M.D., M. Galin, M.D., D. Silverstone, M.D., D. Shin, M.D., Ph.D.)

**Objective:** To evaluate the long-term ocular hypotensive efficacy and the ocular and systemic safety of 0.5% and 1.0% levobunolol ophthalmic solutions b.i.d. compared with 0.5% timolol b.i.d. in a double-masked study in subjects with chronic open-angle glaucoma or ocular hypertension.

**Study Population:**

1. One-hundred-sixty-six subjects with glaucoma or intraocular hypertension were entered into the study (53 on 0.5% and 55 on 1.0% levobunolol and 58 on 0.5% timolol).

2. Thirteen subjects were discontinued because of inadequate control of IOP.
3. Eleven subjects were discontinued for drug unrelated problems.
4. Fifteen subjects (9%) were discontinued for adverse experiences.
5. Four subjects were discontinued for other administrative reasons.

**Study Methods:** This was a parallel, double-masked clinical trial with random assignment of subjects to treatment group. Following a washout interval, medications were instilled b.i.d. in both eyes. All variables were evaluated at baseline and frequently over a 15 month period.

**Efficacy Results:**

1. At all follow-up visits, mean reductions in IOP ranged from 6.09 mm Hg to 9.77 mm Hg in all three treatment groups. At all follow-up visits, the reductions in IOP within all treatment groups was significant with an overall mean IOP reduction of 7.97 mm Hg for 0.5% timolol, 7.95 mm Hg for 0.5% levobunolol, and 8.20 mm Hg for 1.0% levobunolol (Table 2).

**Table 2**

Intraocular Pressure (mmHg): Changes from Baseline  
Conventional Analysis

Day	0.5% Timolol			0.5% Levobunolol			1.0% Levobunolol			Among-group p-values*
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
1 (baseline)	56	27.34	5.18	52	26.57	2.90	54	27.52	3.57	NS
4	43	-8.34**	3.59	39	-8.65	3.68	39	-7.77	3.37	NS
8	38	-8.61	3.73	38	-8.50	3.59	40	-7.90	2.80	NS
15	40	-7.35	2.76	37	-8.03	3.01	39	-8.46	4.09	NS
29	25	-7.72	2.33	27	-8.28	2.42	30	-8.20	4.20	NS
43	32	-8.19	3.20	31	-8.84	3.18	35	-8.33	4.29	***
57	33	-8.38	2.98	35	-9.01	4.10	41	-8.94	4.16	***
85	26	-7.98	3.00	30	-7.27	3.15	29	-9.02	4.50	NS
113	36	-8.15	3.38	41	-8.01	2.83	39	-8.68	3.89	***
169	37	-7.66	2.81	35	-6.89	3.77	38	-8.22	4.42	NS
260	32	-7.33	3.47	29	-7.93	3.81	30	-8.03	3.59	NS
337	27	-7.02	3.53	20	-6.52	3.95	25	-7.32	4.28	NS
435	16	-6.09	2.33	12	-6.17	2.68	15	-9.77	5.35	0.008
<b>OVERALL MEAN</b>		<b>-7.97</b>			<b>-7.95</b>			<b>-8.20</b>		<b>NS</b>

\* Multiple Comparisons:

MEAN decrease in 1.0% levobunolol significantly greater than 0.5% levobunolol or 0.5% timolol

\*\* All treatment groups showed significant within-group decreases from baseline (p < 0.001)

2. Of the 162 subjects evaluated for efficacy, 9% of the timolol group, 8% of the 0.5% levobunolol group, and 7% of the 1.0% levobunolol group were terminated from the study because of inadequately controlled IOP.

### Safety Results

1. Heart Rate: Twenty-seven subjects in the timolol group, 27 subjects in the 0.5% levobunolol group and 35 subjects in the 1.0% levobunolol group showed decreases in heart rate  $> 15\%$  at one or more follow-up visits.
2. Systolic blood pressure: Clinically significant decreases ( $> 20$  mm Hg) occurred in 22 subjects on 0.5% timolol, in 23 subjects on 0.5% levobunolol and in 23 subjects in the 1.0% levobunolol group at one or more follow-up visits.
3. Diastolic blood pressure: Clinically significant decreases ( $> 10$  mm Hg) occurred in 27 subjects on 0.5% timolol, 28 subjects on 0.5% levobunolol, and in 28 subjects in the 1.0% levobunolol group.
4. Observed changes in visual acuity, pupil size, corneal sensitivity, biomicroscopy, and ophthalmoscopy were minimal, similarly distributed between the levobunolol and timolol treatment groups and within the range of normal variation routinely observed in subjects with glaucoma.
5. Subjective complaints: The commonest complaint was burning, stinging and/or irritation at one or more visits evenly distributed in the three treatment groups.

**Conclusion:** The ocular hypotensive efficacy of 0.5% and 1.0% Levobunolol were similar to that of 0.5% timolol. Approximately 90% of levobunolol and timolol treated subjects were successfully controlled for one year, with no significant difference among the treatment groups. Approximately 9% of the original treatment groups did not continue in the study due to non-life-threatening drug related adverse reactions.

### C. Protocol No. LBUN-112-6617

#### Investigators

Manuel Ober, M.D.  
Armin Scharrer, M.D.  
Augenurete-Gemeinschaftspraxis  
Hallerstrasse 2  
Furth  
West Germany

Robert David, M.D.  
Department of Ophthalmology  
Bar-Sheiba  
Israel

**Objective:** To compare the long-term ocular hypotensive efficacy and the ocular and systemic safety of 0.5% and 1.0% levobunolol ophthalmic solution b.i.d. with 0.5% Timolol in subjects with open-angle glaucoma or ocular hypertension.

**Results:** This study was incomplete at the time of submission of this NDA. Only 47 subjects of an original group of 92 had completed 48 weeks of the study. In these subjects there were no significant differences in the pressure reduction efficacy of the three treatment groups and no life-threatening adverse reactions.

#### IV. Special Studies

##### A. Protocol No. LBUN 113-6617

**Investigators:** H. J. Merte, M.D.  
Augenlinik and Poliklinik  
Rechts der Isar der  
Technischen Universität  
München, Federal Republic of Germany

Moshe Lazar, M.D.  
Ichilov Medical Center  
Tel Aviv  
Israel

**Objective:** To investigate the safety and efficacy of L-bunolol in reducing ocular pressure in patients with open-angle glaucoma or ocular hypertension over a 6-month period.

**Study Method:** The study was double-masked with subjects randomized into three parallel groups so that both eyes of each patient will receive b.i.d. treatment with solutions of 0.5% bunolol, 1.0% bunolol, or 0.5% timolol as a positive control.

**Results:** A mean ocular hypotensive effect of 5.3 to 6.4 mm Hg was apparent in all three treatment groups within four days after treatment initiation and remained in this range for the entire study period. A complete statistical summary for this study was not provided. The sponsor felt that the study did not meet good clinical practice standards.

**B. Protocol No. LBUN 116-6549**

Investigators: Arthur Charap, Ph.D., M.D.  
Allergan Pharmaceuticals  
2525 Dupont Drive  
Irvine, California 92713

Objective: To determine whether a measurable change in corneal anesthesia can be appreciated with the Lunau esthesiometer following a single drop instillation of 2% L-bunolol.

Study Method: Open label and unmasked.

Number of Subjects: Eight normal volunteers.

Results: Slight decreases in corneal sensitivity were seen in an unspecified number of volunteers after the instillation of a single drop of 2.0% levobunolol solution.

Summary: A total of 726 subjects participated in 10 clinical trials, conducted at 22 sites, designed to assess the safety and efficacy of levobunolol hydrochloride (Betagan Liquifilm Ophthalmic Solution) in the treatment of glaucoma. The subjects ranged in age from 18 to 93 years, and were divided equally between the sexes. Twenty subjects were normal volunteers and 708 had elevated intraocular pressure. All of the subjects with normal eyes participated in one day studies, while most of the subjects with elevated intraocular pressure were treated for extended periods of time (3 to 15 months), with either 0.25%, 0.5%, or 1.0% levobunolol or 0.5% timolol. Overall, the clinical studies were generally double-masked, randomized, positively controlled (0.5% timolol) clinical trials:

One-drop, dose range finding studies (LBUN-101-6617 and LBUN-102-6617) showed that 0.6% and 1.0% levobunolol produced significant reductions in intraocular pressure for up to 16 hours (0.6%) and 24 hours (1.0%). Significant change in blood pressure (systolic and diastolic) did not occur with drug concentrations of less than 2.0%, but heart rate is significantly reduced by 1.0% levobunolol.

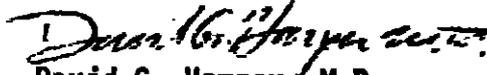
Three month efficacy, safety and dose titration studies (LBUN-103-6617, LBUN-104-6617, LBUN 110-6617) were carried out. In the only placebo controlled study (LBUN 103-6617) 0.5% and 1.0% levobunolol produced mean IOP reductions from baseline that ranged from 7.15 to 11.27 mm Hg, whereas placebo produce only minor alterations in IOP. This study also demonstrated satisfactory control of IOP in 92% of patients on 1.0% and in 86% of patients on 0.5% levobunolol. In study LBUN 104-6617, 52% of levobunolol and 31% of the timolol groups showed clinically significant decreases in heart rate (> 15%) at one or more follow-up visits. Effects on blood pressure in these studies were minimal and of limited clinical significance. Study LBUN 110-6617 was incomplete at the time the NDA was filed.

Two long-term (15 month) safety and efficacy studies (LBUN-105-6617 and LBUN-106-6617) were carried out comparing 0.5% and 1.0% levobunolol with 0.5% timolol. Both studies demonstrated that levobunolol is comparable to timolol in both safety and efficacy and that the efficacy of 0.5% levobunolol is statistically equal to 1.0% levobunolol.

Labeling Review: General labeling claims were reviewed and found to be satisfactory. However, use of the 0.25% dosage form was evaluated in only one study (LBUN-104-6617) in which 15 of 24 subjects (63%) were controlled with this strength.

Conclusion: The studies adequately support the safety and efficacy of 0.5% and 1.0% Betagan Liquifilm Sterile Ophthalmic Solution (levobunolol hydrochloride) in the treatment of chronic glaucoma. This drug is expected to have safety and efficacy parameters similar to TIMOPTIC (timolol maleate).

Recommendation: 0.5% and 1.0% Betagan Liquifilm Sterile Ophthalmic Solution (NDA 19-219), for the treatment of glaucoma, is recommended for approval.

  
David G. Harper, M.D.

cc:

Or 1g NDA

HFN-815

HFN-815/CSO

HFN-340

HFN-815/LGHarper:js/1/28/85

2917b

Advertisement of Review of NDA 19-219

March 23, 1985

Protocol No. LBUN-105-6617

Page 8: The eight subjects disqualified for adverse experiences were included in the safety evaluation.

Page 9: Overall, mean decreases in heart rate were significantly greater in the 1.0% levobunolol group than in the 0.5% Timolol or 0.5% levobunolol group (Vol. 15, page 62, Table 14):

	<u>0.5 Timolol</u>	<u>0.5% Levobunolol</u>	<u>1.0 Levobunolol</u>
Overall Mean Heart Rate	-4.32	-5.63	-9.47

Page 12: There were not significant differences in the degree of blood pressure changes between the groups (Vol. 15, page 65, Table 16 and Vol. 15, page 67, Table 18).

Page 11: The sponsor was asked to compare the standard deviations for IQP between the 0.5% and the 1.0% levobunolol groups (LBUN-106-6617). They responded by stating, "Although by visual inspection, the standard deviations for the 1% groups appeared larger than for the 0.5% groups. These, when examined by Allergan's Biostatistics Department were found to be not significantly different after correcting for multiple tests over time."

A safety update on long-term studies LBUN-105-6617, LBUN-106-6617 and LBUN-112-6617 was applied by the sponsor on March 15, 1985. The number of patients discontinued due to adverse experiences since the submission of the original NDA are as follows:

LBUN-105-6617 - 9 patients (6.3%)  
LBUN-106-6617 - 15 patients (5.5%)  
LBUN-112-6617 - 5 patients (5.8%)

The majority of the discontinuations were due to minor but annoying local side effects such as itching and swelling of eyelids, edema and other local conjunctival reactions. However, eight patients (29%) were discontinued because of cardiac or respiratory problems, none recorded as life-threatening.

David G. Harper, M.D.

cc:  
Orig NDA  
HFN-815  
HFN-815/CSO  
HFN-340  
HFN-815/DGHarper:js/3/23/85  
3481b

CHEM

REV

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

HFU-815

CHEMIST'S Review

NDA 19-219

Date: June 14, 1984

APPLICANT:

Allergan  
2525 Dupont Drive  
Irvine, CA 92713

NAMES:

Proprietary  
USAN  
Other

Betagan<sup>TM</sup>  
Levobunolol Hydrochloride

1

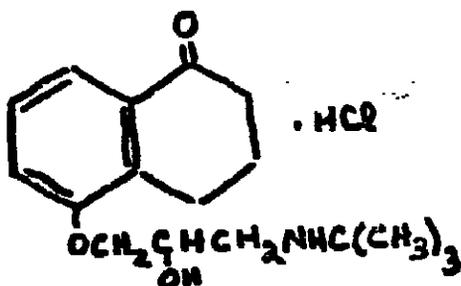
DOSEAGE FORM AND ROUTE OF ADMINISTRATION:

Liquifilm<sup>R</sup> sterile ophthalmic solution  
0.25%, 0.5%, 1.0%

PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION:

Noncardioselective beta-adrenoceptor blocking agent.  
Control of intraocular pressure (IOP) in chronic  
open-angle glaucoma and ocular hypertension.

STRUCTURAL FORMULA AND CHEMICAL NAMES:



C<sub>17</sub>H<sub>25</sub>NO<sub>3</sub> · HCl

MW 327.85

- (1) 1 (2H)-Naphthalenone, 5- [3- [(1,1-dimethylethyl)amino] -2-hydroxypropyl] -3,4-dihydro- hydrochloride. (-)
- (2) (-)-5- [3-(tert-Butylamino)-2-hydroxypropoxy] -3,4-dihydro- 1 (2H)-naphthalenone hydrochloride

INITIAL SUBMISSION:

dated: January 17, 1984  
received: January 19, 1984  
assigned: May 24, 1984

SUPPORTING DOCUMENTS:

0  
1

REMARKS:

Storage cautions on labeling, should specify a temperature limit rather than "excessive heat"

CONCLUSIONS/RECOMMENDATIONS:

CC: ~~orig~~ NDA  
EFN-815  
EFN-815/CSO  
EFN-815/ARCasola  
EFN-815/MAJaraki  
EFN-616

*Mary Ann Jaraki 6/14/84*  
Mary Ann Jaraki  
Chemist EFN-815

*McC Glistey*

NDA 19-219  
Review Notes

COMPONENTS - Dosage Forms:

Adequate

COMPOSITION:

Adequate

FACILITIES AND PERSONNEL:

Adequate

e:

Description:

Components of the synthesis are listed and Material Specifications are provided for each ingredient. They are adequate. :)

Remarks:

Stability Data is included for the NDS as follows:

Remarks:

There is no indication of instability from the data presented. However, it is to be noted that the data is only two point data, that is initial and at the end of the storage period.  
The TLC determination for 5-hydroxy-3,4-dihydro-1(2H)naphthalenone was not performed.

The DAF Holder proposes a 5 year expiration date for the NDS.

Comment:

**LABELING:**

Adequate with reservation

Storage cautions on labeling are not yet resolved. The storage caution on labels relating to heat should specify a temperature limit and both heat and light cautions should be supported by data (see comments relating to stability)

**ESTABLISHMENT INSPECTION:**

Requested (- )

**Rx STATEMENT**

Included

**PART 12 2:**

Included

**ENVIRONMENTAL IMPACT:**

Included

If the product is to be disposed of, it will be disposed of in the water waste system. Allergan states that the water waste system has the capability of handling this type of waste.

The applicant states that the action will provide a health product, and an analysis has shown no significant risks to the environment. Therefore, the benefit does outweigh the potential risks to the environment.

**Comment:**

The applicant is to clarify whether applicable Federal, State and Local Regulations are met.

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS  
NPN-815  
CHEMIST'S REVIEW

NDA 19-219

Date: February 21, 1985

APPLICANT:

Allergan  
2525 Dupont Drive  
Irvine, CA 92713

NAME:

Proprietary:  
USAN:

Betagen<sup>TM</sup>  
Levobunolol hydrochloride

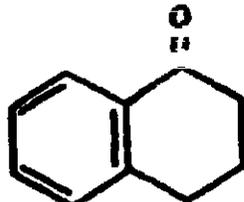
DOSE FORM AND ROUTE OF ADMINISTRATION:

Liquifilm<sup>R</sup>, sterile, ophthalmic solution.  
0.25%, 0.5% and 1.0%.

PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION:

Noncardioselective, beta-adrenoceptor blocking agent  
for control of intraocular pressure in chronic  
open-angle glaucoma and ocular hypertension.

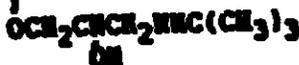
STRUCTURAL FORMULA AND CHEMICAL NAME:



C<sub>17</sub>H<sub>25</sub>NO<sub>3</sub>·HCl

.HCl

N.W. 327.9



(-)-5-[3-(tert-Butylamino)-2-hydroxypropoxy]-3,4-dihydro 1(2H)-naphthalenone hydrochloride

INITIAL SUBMISSION:

dated:

January 17, 1984

received:

January 19, 1984

assigned:

May 24, 1984

AMENDMENTS:

4:

SUPPORTING DOCUMENTS:

1 3  
1 1

5:

NSA 19-219  
Review Notes - Review (

**COMPONENTS AND COMPOSITION:**

Adequate.

**FACILITIES AND PERSONNEL:**

Adequate.

**SYNTHESIS:**

Generally Adequate. (

(  
Comment:

(  
**RAW MATERIAL CONTROLS:**

Now adequate with reservation.

~~Comment~~

**MANUFACTURING AND PROCESSING:**  
(

( )

)

*glt*

2. Twenty three 200 day ...  
stored ... data:

**SAMPLES AND RESULTS:**

Required.

**LABELING:**

*f*

**ESTABLISHMENT INSPECTION:**

Requested

**Rx STATEMENT:**

Adequate.

**PART 12 g:**

Adequate.

**ENVIRONMENTAL IMPACT:**

Now adequate.

A revised environmental impact analysis report is included in the August 29, 1984 resubmission.

REVISION OF ANTI-INECTIVE DRUG PRODUCTS  
NDA-815  
CHEMIST'S REVIEW

Date: June 19, 1985

NDA 19-219

APPLICANT:

Allergan  
2525 Dupont Drive  
Irvine, CA 92713

NAME:

Proprietary:  
USAN:

Betagan<sup>TM</sup>  
Levobunolol hydrochloride  
Also refer to Chemist's Review

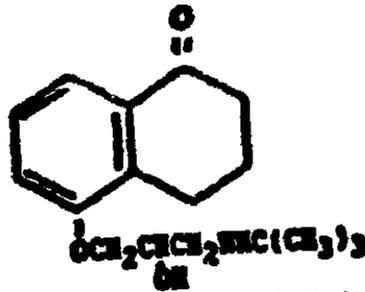
DOSAGE FORM AND ROUTE OF ADMINISTRATION:

Liquifilm<sup>R</sup>, sterile, ophthalmic solution.  
0.25%, 0.5% and 1.0%.

PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION:

Noncardioselective, beta-adrenoceptor blocking agent for control of intraocular pressure in chronic open-angle glaucoma and ocular hypertension.

STRUCTURAL FORMULA AND CHEMICAL NAME:



.HCl

C<sub>17</sub>H<sub>23</sub>NO<sub>2</sub>·HCl

H.W. 327.9

(-)-3-(3-(2R)-butylamino)-7-hydroxypropoxy)-3,4-dihydro 1(2H)-naphthalene hydrochloride

INITIAL SUBMISSION:

dated:  
received:  
assigned

January 17, 1984  
January 19, 1984  
May 24, 1984

AMEND

SUPPORTING DOCUMENTS:

Refer to previous Chemistry Reviews.

**REMARKS:**

Recent submissions have completed the manufacturing and control information for this NDA and the information is acceptable with one exception. The applicant proposes 24 month expiry dates for the products while the Stability Protocol proposes 36 months. The protocol must be amended. Results of validation of NDA methods have been received from the Los Angeles District.

**CONCLUSIONS AND RECOMMENDATIONS:**

The application is basically in accord with Section 505(b) of the Act in relation to manufacturing and control procedures. However, the CSO should call the applicant and request a revised Stability Protocol (as above), and evaluation of methods by the Division of Drug Chemistry should be completed before final approval of the 'Chemistry Section' is given.

cc: orig NDA  
~~MFN-815~~  
MFN-815/CSO  
MFN-815/ARCasola  
MFN-815/MAJarski  
MFN-815/MD  
B/D init. by AR Casola

*Mary Ann Jarski 6/19/85*  
Mary Ann Jarski  
Chemist MFN-815

*Rec 6/21/85*

**EDA 19-219**  
**Review Notes**

**NOTE: These Review Notes only cover those sections which were previously incomplete.**

**SYNOPSIS:**

**Now Acceptable**

*[Handwritten mark]*

**RAW MATERIAL CONTROLS:**

**Now Acceptable**

*[Handwritten mark]*

**CONTAINERS:**

**Now Acceptable**

*[Handwritten mark]*

**LABORATORY CONTROLS:**

**Now Acceptable**

**NDA 19-219**  
**Review Notes**

- System suitability data were included in the submission of 3-7-85. Methods were sent to FDA laboratories for validation on 4-1-85.

**STABILITY:**

Now Acceptable <sup>f</sup>

07/5

et

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**Comment:**

This product will carry a 24 mo. expiry date not a 30 month expiry date. The applicant is to revise the protocol accordingly.

**TABLE I****Data for Levobunolol HCl Lots Under Heat Stress (45°C)****1% Levobunolol HCl (Lot 5832A)**

<u>Age (days)*</u>	<u>Levobunolol HCl (% w/v)</u>	<u>Benzalkonium Chloride (% w/v x 100)</u>	<u>pH</u>	<u>Physical Appearance</u>	<u>USP Preservative Effectiveness</u>
Initial	1.06	0.451	6.95	Meets test	---
34	1.05	---	6.06	Meets test	---
58	1.05	---	5.96	Meets test	---
90	1.04	---	5.91	Meets test	---
121	1.06	0.339	5.72	Meets test	Pass

**1% Levobunolol HCl (Lot 6187C)**

<u>Age (days)*</u>	<u>Levobunolol HCl (% w/v)</u>	<u>Benzalkonium Chloride (% w/v x 100)</u>	<u>pH</u>	<u>Physical Appearance</u>	<u>USP Preservative Effectiveness</u>
Initial	1.07	0.356	6.83	Meets test	---
64	1.05	0.405	5.80	Meets test	---
120	1.05	0.355	5.59	Meets test	---
182	---	---	---	---	Pass

**1% Levobunolol HCl (Lot 6167D)**

<u>Age (days)*</u>	<u>Levobunolol HCl (% w/v)</u>	<u>Benzalkonium Chloride (% w/v x 100)</u>	<u>pH</u>	<u>Physical Appearance</u>	<u>USP Preservative Effectiveness</u>
Initial	1.07	0.364	6.3	Meets test	---
64	1.05	0.389	5.75	Meets test	---
120	1.08	0.358	5.56	Meets test	---
182	1.09	0.420	5.19	Meets test	Pass

**0.5% Levobunolol HCl (Lot 5840A)**

<u>Age (days)*</u>	<u>Levobunolol HCl (% w/v)</u>	<u>Benzalkonium Chloride (% w/v x 100)</u>	<u>pH</u>	<u>Physical Appearance</u>	<u>USP Preservative Effectiveness</u>
Initial	0.536	0.430	7.01	Meets test	---
34	0.535	---	6.34	Meets test	---
58	0.534	---	6.20	Meets test	---
90	0.530	---	6.05	Meets test	---
121	0.538	0.378	6.00	Meets test	Pass

\*Days at 5°.

TABLE I (Continued)

Data for Levobunolol HCl Lots Under Heat Stress (45°C)

0.25% Levobunolol HCl (Lot 62598)

<u>Age (days)*</u>	<u>Levobunolol HCl (% w/v)</u>	<u>Benzalkonium Chloride (% w/v x 100)</u>	<u>pH</u>	<u>Physical Appearance</u>	<u>USP Preservative Effectiveness</u>
Initial	0.260	0.380	7.04	Meets test	---
30	0.255	0.393	6.54	Meets test	---
62	0.258	0.388	6.28	Meets test	---
90	0.261	0.396	6.14	Meets test	---
120	---	0.405	6.12	Meets test	Pass
141	---	0.416	---	---	---
162	0.261	---	---	---	---

0.25% Levobunolol HCl (Lot 6259C)

<u>Age (days)*</u>	<u>Levobunolol HCl (% w/v)</u>	<u>Benzalkonium Chloride (% w/v x 100)</u>	<u>pH</u>	<u>Physical Appearance</u>	<u>USP Preservative Effectiveness</u>
Initial	0.260	0.377	7.06	Meets test	---
30	0.256	0.394	6.60	Meets test	---
62	0.253	0.398	6.28	Meets test	---
90	0.255	0.401	6.18	Meets test	---
120	---	0.398	6.15	Meets test	Pass
141	---	0.404	---	---	---
162	0.257	---	---	---	---

0.25% Levobunolol HCl (Lot 6259D)

<u>Age (days)*</u>	<u>Levobunolol HCl (% w/v)</u>	<u>Benzalkonium Chloride (% w/v x 100)</u>	<u>pH</u>	<u>Physical Appearance</u>	<u>USP Preservative Effectiveness</u>
Initial	0.259	0.371	7.05	Meets test	---
30	0.254	0.398	6.58	Meets test	---
62	0.253	0.397	6.31	Meets test	---
90	0.258	0.390	6.15	Meets test	---
120	---	0.382	6.13	Meets test	Pass
162	0.251	---	---	---	---

\*Days at 45°.

**TABLE I (Continued)**

**Data for Levobunolol HCl Lots Under Heat Stress (45°C)**

**0.25% Levobunolol HCl (Lot 6259E)**

<u>Age (days)*</u>	<u>Levobunolol HCl (% w/v)</u>	<u>Benzalkonium Chloride (% w/v x 100)</u>	<u>pH</u>	<u>Physical Appearance</u>	<u>USP Preservative Effectiveness</u>
Initial	0.259	0.381	7.06	Meets test	---
30	0.255	0.398	6.58	Meets test	---
62	0.253	0.395	6.34	Meets test	---
90	0.252	0.393	6.13	Meets test	---
120	---	0.306	6.14	Meets test	Pass
162	0.252	---	---	---	---

\*Days at 45°.

**TABLE II****Data for Levobunolol HCl Lots under Light Stress\***

<u>Product</u>	<u>Lot #</u>	<u>F111 Volume (cc)</u>	<u>Container Size (cc)</u>
1.0%	6617X-001	5	10
0.5%	6618X-001	5	10
0.25%	6711X-001	5	10

**1% Levobunolol HCl (Lot 6617X-001)**

<u>Age (days)**</u>	<u>Levobunolol HCl (% w/v)</u>	<u>pH</u>	<u>Physical Appearance</u>
Initial	1.03	7.02	Meets test
17	1.04	6.63	Meets test
37	1.03	6.51	Meets test
56	1.03	—	Meets test
188	1.05	6.20	Meets test
387	1.06	6.26	Meets test
776	1.08	5.97	Meets test

**0.5% Levobunolol HCl (Lot 6618X-001)**

<u>Age (days)**</u>	<u>Levobunolol HCl (% w/v)</u>	<u>pH</u>	<u>Physical Appearance</u>
Initial	0.512	7.04	Meets test
23	0.506	—	Meets test
37	0.516	6.74	Meets test
56	0.516	—	Meets test
188	0.516	6.50	Meets test
387	0.524	6.43	Meets test
776	0.540	6.13	Meets test

**0.25% Levobunolol HCl (Lot 6711X-001)**

<u>Age (days)**</u>	<u>Levobunolol HCl (% w/v)</u>	<u>pH</u>	<u>Physical Appearance</u>
Initial	0.256	7.12	Meets test
23	0.254	—	Meets test
37	0.252	6.87	Meets test
56	0.253	—	Meets test
188	0.260	6.69	Meets test
387	—	6.56	Meets test
776	0.266	6.24	Meets test

\* Approximately 75 Foot-candle intensity  
 \*\*Days of light exposure

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

BN-815

CHEMIST'S REVIEW

NEA 19-219

Date: July 19, 1985

APPLICANT:

Allergan  
2525 Dupont Drive  
Irvine, CA 92713

NAME:

Proprietary:  
NAME:

Betagan<sup>TM</sup>  
Levobunolol hydrochloride  
Also refer to Chemist's Review # 1

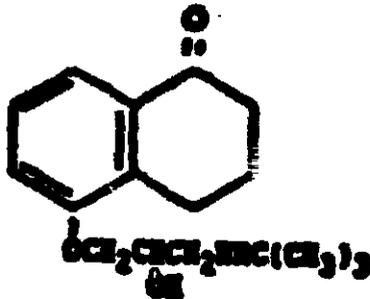
DOSE FORM AND ROUTE OF ADMINISTRATION:

Liquifilm<sup>R</sup>, sterile, ophthalmic solution.  
0.25%, 0.5% and 1.0%.

PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION:

Noncardioselective, beta-adrenoreceptor blocking agent for control of intraocular pressure in chronic open-angle glaucoma and ocular hypertension.

STRUCTURAL FORMULA AND CHEMICAL NAME:



(-)-1-[3-(1,2-dipropylamino)-2-hydroxypropoxy]-3,4-dihydro 1(2H)-naphthalene hydrochloride

INITIAL SUBMISSION:

dated:	January 17, 1984
received:	January 19, 1984
assigned:	May 24, 1984

AMENDMENTS:

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SUPPORTING DOCUMENTS:

dated:

Refer to Chemist's Review

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REMARKS:

RECOMMENDATIONS AND CONCLUSIONS:

The application is in accord with Section 505(b) of the Act in relation to manufacturing and control procedures and may be approved from this standpoint.

*Mary Ann Jarski 7/19/85*  
Mary Ann Jarski  
Chemist HFN-815

*ARC 7/19/85*

cc: Orig NDA

HFN-815

HFN-815/MD'

HFN-815/CSO

HFN-815/MAJarski

R/D initialed by: ARCasola 7/19/85

**SUMMARY BASIS OF APPROVAL**

**III. Manufacturing and Control:**

Manufacturing and controls, stability, methods validation, labeling, inspections, and environmental impact evaluation conform to all Federal Register regulations.