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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-270

AUG 30 1985

Mr. Lou Horger
Alcon Laboratories
P.O. Box 1959
6201 South Freeway
Fort Worth, TX 76101

Dear Mr. Horger:

Reference is made to your New Drug Application dated April 26, 1985 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Betoptic (betaxolol hydrochloride) Ophthalmic Solution.

The application was filed on May 6, 1985.

We acknowledge your June 4, 1985 letter notifying us of your commitment to conduct a repeat two-year carcinogenicity study in mice. The protocol should be reviewed by the Division of Anti-Infective Drug Products before its initiation.

We also acknowledge your commitment, as discussed in a telephone conversation with Dr. Bilstad on August 30, 1985, to conduct a phase IV post-marketing study to provide additional safety information about Betoptic Ophthalmic Solution. The details of the study should be discussed with FDA staff and a protocol should be prepared and submitted to the Agency within 3 months.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling, including the changes in your letter of August 29, 1985, provided that the following additional changes be made in the labeling prior to marketing the drug:

1. Indications and Usage, revise second paragraph to read:

   In clinical studies Betoptic safely controlled the intraocular pressure of 47 patients with glaucoma and reactive airway disease followed for a mean period of 15 months. However, caution should be used in treating patients with severe reactive airway disease.

2. Contraindications, sentence 2, delete the words "a history of".

3. Warnings, revise to read:

   Although Betoptic Ophthalmic Solution has had little or no effect on heart rate or blood pressure in clinical studies, caution should be observed in treating patients with a history of cardiac failure. Treatment with Betoptic Ophthalmic Solution should be discontinued at the first signs of cardiac failure.

Accordingly, the application is approved.

In addition, we would appreciate your submitting in duplicate the advertising copy which you intend to use in your proposed promotional or advertising campaign. Please submit one of the copies directly to the Division of Drug Advertising with a copy of the package insert.

We remind you that you must comply with the requirements set forth under CFR 314.80 and 314.81 for an approved NDA.

Your cooperation is appreciated.

Sincerely yours,

Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

cc: DAL-DO
ORIG. NDA 19-270
HFN-800/JMinor
HFN-82
HFN-710
HFN-220
~~HFN-815/CSO/RLinkous/sdj~~/5/17/85 HFN-815/MO/DHarper/5/23/85
HFN-815/CHEM/JTaylor/5/23/85 HFN-815/PHARM
R/D init. by: ETabor/5/30/85/F/T init: 6/17/85/6/26/85
ARCasola/5/23/85/F/T init: 6/17/85/6/25/85
JMDavitt/5/23/85/F/T init: 6/17/85/6/25/85
SJoshi/5/23/85/6/25/85
GRStanley/F/T init.: 6/17/85/6/25/85
F/T: 6/11/85/8/30/85
4030b

APPROVED

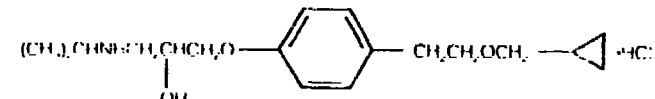
ET 8/30/85


FPL

Betoptic™

(betaxolol hydrochloride)
0.5% as base
Sterile Ophthalmic Solution

DESCRIPTION BETOPTIC™ Sterile Ophthalmic Solution contains betaxolol hydrochloride, a cardioselective beta-adrenergic receptor blocking agent, in a sterile isotonic solution. Betaxolol hydrochloride is a white crystalline powder, soluble in water, with a molecular weight of 343.89. The chemical structure is presented below:



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

Chemical Name:
(±)-1-[p-[2-(Cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol hydrochloride

Each ml of BETOPTIC Ophthalmic Solution, (0.5%) contains: Active: 5.6 mg betaxolol hydrochloride equivalent to betaxolol base 5 mg. Preservative: Benzalkonium Chloride 0.01%. Inactive: Edetate Disodium, Sodium Chloride, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), and Purified Water. DM 20

CLINICAL PHARMACOLOGY: Betaxolol HCl, a cardioselective (beta-1-adrenergic) receptor blocking agent, does not have significant membrane-stabilizing (local anesthetic) activity and is devoid of intrinsic sympathomimetic action. Orally administered beta-adrenergic blocking agents reduce cardiac output in healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function beta-adrenergic receptor antagonists may inhibit the sympathetic stimulatory effect necessary to maintain adequate cardiac function.

When instilled in the eye, BETOPTIC Ophthalmic Solution has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Ophthalmic betaxolol has minimal effect on pulmonary and cardiovascular parameters.

Ophthalmic betaxolol (one drop in each eye) was compared to timolol and placebo in a three-way masked cross-over study challenging patients with reactive airway disease. Betaxolol HCl had no significant effect on pulmonary function as measured by Forced Expiratory Volume in one second (FEV_1), Forced Vital Capacity (FVC) and FEV_1/VC. Additionally, the action of isoproterenol, a beta stimulant, administered at the end of the study was not inhibited by ophthalmic betaxolol. In contrast, ophthalmic timolol significantly decreased these pulmonary functions.

FEV_1–Percent Change from Baseline[1]

	Means		
	Betaxolol 1.0%[a]	Timolol 0.5%	Placebo
Baseline	1.6	1.4	1.4
60 Minutes	2.3	−25.7*	5.8
120 Minutes	1.6	−27.4*	7.5
240 Minutes	−6.4	−26.9*	6.9
Isoproterenol[b]	36.1	−12.4*	42.8

[1]Schoene, R. B., *et al* Am. J. Ophthal. 97:86, 1984.
[a]Twice the clinical concentration.
[b]Inhaled at 240 minutes; measurement at 270 minutes.
*Timolol statistically different from betaxolol and placebo ($p<0.05$).

No evidence of cardiovascular beta adrenergic-blockade during exercise was observed with betaxolol HCl in a double-masked, three-way crossover study in normal subjects comparing ophthalmic betaxolol, timolol and placebo for effects on blood pressure and heart rate. Mean arterial blood pressure was not affected by any treatment; however, ophthalmic timolol produced a significant decrease in the mean heart rate.

Mean Heart Rates[1]

	TREATMENT		
Bruce Stress Exercise Test Minutes	Betaxolol 1%[a]	Timolol 0.5%	Placebo
0	79.2	79.3	81.2
2	130.2	126.0	130.4
4	133.4	128.0*	134.3
6	136.4	129.2*	137.9
8	139.8	131.8*	139.4
10	140.8	131.8*	141.3

[1]Atkins, J. M., Pugh, B. R. Jr., and Timewell, R. M.: Cardiovascular Effects of Topical Beta-Blockers During Exercise. Am. J. Oph. 99:173-175, Feb., 1985.
[a]Twice the clinical concentration.
*Mean pulse rate significantly lower for timolol than betaxolol or placebo ($p<0.05$).

Clinical Studies: Optic nerve head damage and visual field loss are the result of a sustained elevated intraocular pressure and poor ocular perfusion. BETOPTIC Ophthalmic Solution has the action of reducing elevated as well as normal intraocular pressure and the mechanism of ocular hypotensive action appears to be a reduction of aqueous production as demonstrated by tonography and aqueous fluorophotometry. The onset of action with BETOPTIC Ophthalmic Solution can generally be noted within 30 minutes and the maximal effect can usually be detected 2 hours after topical administration. A single dose provides a 12-hour reduction in intraocular pressure. Clinical observation of glaucoma patients treated with BETOPTIC Ophthalmic Solution for up to three years shows that the intraocular pressure lowering effect is well maintained.

Clinical studies show that topical BETOPTIC Ophthalmic Solution reduces mean intraocular pressure 25% from baseline. In trials using 22 mmHg as a generally accepted index of intraocular pressure control, BETOPTIC Ophthalmic Solution was effective in more than 94% of the population studied, of which 73% were treated with the beta blocker alone. In controlled, double-masked studies, the magnitude and duration of the ocular hypotensive effect of BETOPTIC Ophthalmic Solution and ophthalmic timolol solution were clinically equivalent.

BETOPTIC Ophthalmic Solution has also been used successfully in glaucoma patients who have undergone a laser trabeculoplasty and have needed additional long-term ocular hypotensive therapy.

BETOPTIC Ophthalmic Solution has been well-tolerated in glaucoma patients wearing hard or soft contact lenses and in aphakic patients.

BETOPTIC Ophthalmic Solution does not produce miosis or accommodative spasm which are frequently seen with miotic agents. The blurred vision and night blindness often associated with standard miotic therapy are not associated with BETOPTIC Ophthalmic Solution. Thus, patients with central lenticular opacities avoid the visual impairment caused by a constricted pupil.

INDICATIONS AND USAGE: BETOPTIC™ Ophthalmic Solution has been shown to be effective in lowering intraocular pressure and is indicated in the treatment of:

1. Patients with chronic open-angle glaucoma
2. Patients with elevated intraocular pressure (ocular hypertensive patients)
3. Patients with glaucoma or ocular hypertension who have reactive airway disease
4. Patients with glaucoma or ocular hypertension who are currently on multiple anti-glaucoma therapy

CONTRAINDICATIONS: Hypersensitivity to any component of this product.

BETOPTIC Ophthalmic Solution is contraindicated in patients with sinus bradycardia greater than a first degree block, cardiogenic shock, or patients with a history of overt cardiac failure.

PRECAUTIONS: Patients who are receiving a beta-adrenergic blocking agent orally and BETOPTIC Ophthalmic Solution should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

While BETOPTIC Ophthalmic Solution has demonstrated a low potential for systemic effects, it should be used with caution in patients with diabetes (especially labile diabetes) or in patients suspected of developing thyrotoxicosis.

Consideration should be given to the gradual withdrawal of beta adrenergic blocking agents prior to general anesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli.

Pulmonary: BETOPTIC Ophthalmic Solution, a cardioselective beta-blocker, has produced only minimal effects in patients with reactive airway disease, however, caution should be exercised in the treatment of patients with excessive restriction of pulmonary function.

Drug Interactions: Although BETOPTIC Ophthalmic Solution used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with BETOPTIC Ophthalmic Solution and epinephrine has been reported occasionally. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs.

Ocular: In patients with angle-closure glaucoma, the immediate treatment objective is to re-open the angle by constriction of the pupil with a miotic agent. Betaxolol has no effect on the pupil, therefore, BETOPTIC Ophthalmic Solution should be used with a miotic to reduce elevated intraocular pressure in angle-closure glaucoma.

As with the use of other antiglaucoma drugs, diminished responsiveness to BETOPTIC Ophthalmic Solution after prolonged therapy has been reported in some patients. However, in one long-term study in which 25C patients have been followed for up to three years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

ANIMAL STUDIES: No adverse ocular effects were observed following topical ocular administration of BETOPTIC Ophthalmic Solution to rabbits for one year.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Lifetime studies with betaxolol HCl have been completed in mice at oral doses of 6, 20 or 60 mg/kg/day and in rats at 3, 12 or 48 mg/kg/day. betaxolol HCl demonstrated no carcinogenic effect. Higher dose levels were not tested. In a variety of *in vitro* and *in vivo* bacterial and mammalian cell assays, betaxolol HCl was nonmutagenic.

Pregnancy Category C: Reproduction, teratology, and peri- and post-natal studies have been conducted with orally administered betaxolol HCl in rats and rabbits. There was evidence of drug related post-implantation loss in rabbits and rats at dose levels above 12 mg/kg and 128 mg/kg, respectively. Betaxolol HCl was not shown to be teratogenic, however, and there were no other adverse effects on reproduction at subtoxic dose levels. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly indicated.

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

Usage in Children: Clinical studies to establish the safety and efficacy in children have not been performed.

ADVERSE REACTIONS: The following adverse reactions have been reported in clinical trials of up to 3 years of patient experience with BETOPTIC Ophthalmic Solution.

Ocular: BETOPTIC Ophthalmic Solution has been well tolerated. Discomfort of short duration may be experienced by some patients upon installation and occasional tearing has been reported. Rare instances of decreased corneal sensitivity, erythema, itching sensation, corneal punctate staining, keratitis, anisocoria and photophobia have been reported.

Systemic: Systemic reactions following topical administration of BETOPTIC Ophthalmic Solution have been reported rarely (e.g., insomnia and depressive neurosis).

OVERDOSAGE: No information is available on overdosage of humans. The oral LD_{50} of the drug ranged from 350-920 mg/kg in mice and 860-1050 mg/kg in rats. The symptoms which might be expected with an overdose of a systemically administered beta-1-adrenergic receptor blocker agent are bradycardia, hypotension and acute cardiac failure.

A topical overdose of BETOPTIC Ophthalmic Solution may be flushed from the eye(s) with warm tap water.

DOSAGE AND ADMINISTRATION: The usual dose is one drop of BETOPTIC Ophthalmic Solution in the affected eye(s) twice daily. In some patients, the intraocular pressure lowering response to BETOPTIC Ophthalmic Solution may require a few weeks to stabilize. Clinical follow-up should include a determination of the intraocular pressure during the first month of treatment with BETOPTIC Ophthalmic Solution. Thereafter, intraocular pressures should be determined on an individual basis at the judgment of the physician.

When a patient is transferred from a single anti-glaucoma agent, continue the agent already used and add one drop of BETOPTIC Ophthalmic Solution in the affected eye(s) twice a day. On the following day, discontinue the previous anti-glaucoma agent completely and continue with BETOPTIC Ophthalmic Solution.

Because of diurnal variations of intraocular pressure in individual patients, satisfactory response to twice a day therapy is best determined by measuring intraocular pressure at different times during the day. Intraocular pressures <22 mmHg may not be optimal for control of glaucoma in each patient; therefore, therapy should be individualized.

If the intraocular pressure of the patient is not adequately controlled on this regimen, concomitant therapy with pilocarpine, other miotics, epinephrine or systemically administered carbonic anhydrase inhibitors can be instituted.

When a patient is transferred from several concomitantly administered anti-glaucoma agents, individualization is required. Adjustment should involve one agent at a time made at intervals of not less than one week. A recommended approach is to continue the agents being used and add one drop of BETOPTIC Ophthalmic Solution in the affected eye(s) twice a day. On the following day, discontinue one of the other anti-glaucoma agents. The remaining anti-glaucoma agents may be decreased or discontinued according to the patient's response to treatment. The physician may be able to discontinue some or all of the other anti-glaucoma agents.

HOW SUPPLIED: BETOPTIC Ophthalmic Solution is a sterile, isotonic, aqueous solution of betaxolol hydrochloride.

BETOPTIC Ophthalmic Solution is supplied as follows: 5 and 10 ml in white opaque plastic ophthalmic DROP-TAINER® dispensers.

5 ml: NDC 0065-0245-05
10 ml: NDC 0065-0245-10

STORAGE: Store at room temperature.

Alcon

ALCON LABORATORIES, INC.
Fort Worth, Texas 76134
Printed in USA

...Revised: May 1985


MED
REV

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Medical Officer's Review of NDA 19-270

Date: November 30, 1984

Sponsor: Alcon Laboratories, Inc.
P.O. Box 1959
Fort Worth, Texas 76101

Name of Drug: Generic: Betaxolol Hydrochloride
Code: SL 75212
SL 75212-10
Trade: Betaxolol Ophthalmic Solution 0.5%

Pharmacologic Category: Beta-adrenergic receptor blocking agent

Proposed Indication: Antiglaucoma

Dosage Form and Route of Administration: 0.5% aqueous, isotonic solutions for topical ophthalmic administration.

Related Drug: timolol Maleate (TIMOPTIC) NDA 18-086

Manufacturing Controls: Refer to chemistry review.

Pharmacology: Preclinical ocular pharmacology was studied at Alcon Laboratories, and general pharmacology was studied at the Department of Biology of the Laboratoires d'Etudes de Recherches Synthelabo in France.

Ocular pharmacology studies in rabbits revealed the following:

1. Betaxolol had no effect on pupil size in concentration of 0.125%, 0.25%, 0.5% and 1.0%.

2. Corneal anesthesia from Betazolol occured with dosages above 100 ug per cornea.

3. Intraocular pressure reductions occurred with 0.5%, 0.75% and 2.0% drug solutions, peaking between one and two hours and dissipating completely by six hours. The 0.1% solution caused no significant change in IOP as compared to the vehicle control.

   Studies in preparations of isolated guinea pig atria show that the beta adrenergic blocking potency of Betaxolol is similar to that of propanolol but six to seven times greater than that of metoprolol. The drug, however, is only a very weak blocker of beta-2-adrenoceptors in the guinea pig trachea. Propanolol shows no such selectivity.

   These findings suggested that Betaxolol administered topically to the eye should cause a useful lowering of the intraocular pressure without an effect on the pupil or accommodation. In addition, it was expected to pose less risk to the patient with compromised pulmonary function.

Toxicology: The sponsor reports that extensive reproduction, mutagenicity and carcinogenicity studies of Betaxolol hydrochloride have been carried out. The drug has not been found to be mutagenic or carcinogenic, nor to cause other problems with reproduction in test animals except at very high dose levels.

Ocular toxicology studies have substantiated the safety of Betaxolol Ophthalmic Solution for topical ocular use.

Clinical Background: Betaxolol had not been extensively evaluated prior to the studies initiated by the sponsor in 1980 which are reported in this NDA. The drug is not currently marketed in any foreign country.

Literature References

1. Berrisopi,R, Leibowitz, HM. A New B-Adrenergic Blocking Agent for Treatment of Glaucoma. Arch Ophthalmol 1982; 100:943-46.

   0.25% Betaxolol produced a 30% to 35% decrease below baseline IOP in 12 subjects with chronic open angle glaucoma or intraocular hypertension that was maintained during a one year observation period. Visual acuity and tear secretion remained stable throughout the study period as did blood pressure and pulse rate. Corneal anesthesia was not encountered.

2. Berry DP, VanBuskirk EM, Shields MB. Betaxolol and Timolol: A Comparison of Efficacy and Side Effects. Arch Ophthalmol 1984; 102:42-45.

   Forty-six patients with primary open-angle glaucoma were enrolled in a randomized, double-blind study designed to compare 0.5% Betaxolol hydrochloride and 0.5% timolol maleate. Both drugs were noted to lower intraocular pressure equally effectively, and the incidence of both systemic and ocular side effects were comparable. Corneal sensitivity and tear production were not altered by either drug in a clinically significant way.

Related NDA: Timolol maleate (NDA 18-086), a non-selective beta-adrenergic blocking agent very similar to Betaxolol was approved for marketing in the U.S. in 1978. Although Timolol has become the drug of choice in most cases of chronic open angle glaucoma, especially early in its course, it is essentially contraindicated in patients with asthma and other cardio-pulmonary 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 death in association with cardiac failure, have been reported following administration of TIMOPTIC." Documentation of these 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.

Betaxolol is a selective beta-1 blocking agent with negligible effect on beta-2 receptors located in the pulmonary system, and therefore is potentially more suitable than Timolol for use in patients with obstructive pulmonary diseases. Studies have supported this fact showing that Betaxolol topical eye drops have no significant effect on pulmonary function. Significantly, isoproterenol has been noted to enhance pulmonary function in the presence of Betaxolol 1.0%, while its effect is effectively masked by Timolol 0.5%.

Normal Volunteer Studies

1. Protocol No. 79-E-09 (Judson P. Smith, M.D.): Betaxolol Ophthalmic Solution 0.5%, when used twice a day for 28 days reduced intraocular pressure up to 30%. No clinically remarkable ocular or systemic changes were observed.

2. Protocol No. 79-E-21 (Judson P. Smith, M.D.): The data demonstrates that Timolol 0.5% has a greater potential for producing a reduced pulse rate than Betaxolol 0.5%. Neither drug affected mean arterial blood pressure, nor had an adverse effect on ocular tissues.

3. Protocol No. C-82-24 (Billie R. Pugh, M.D. and James M. Atkins, M.D.): This study compared the effects of 1% Betaxolol, 0.5% Timolol, and placebo. No significant difference in pulse, mean arterial pressure, or double product (heart rate x systolic pressure) were seen between subjects when treated with placebo or with 1% Betaxolol. However, 0.5% Timolol produced significantly reduced heart rates (p 0.05) compared with placebo at 4, 6, 8 and 10 minutes of exercise. No differences in mean arterial pressures were detected after the treatments at any of the time intervals. There were no adverse experiences recorded during this study with the exception of one incident of burning upon instillation of Betaxolol

Dose Response Studies

1. Protocol No. 79-E-10 (Alan I. Mandell, M.D.): Eleven patients were evaluated for efficacy in a double-masked trial of Betaxolol Ophthalmic Solution 0.0625%, 0.125%, 0.25%, 0.5% and placebo eyedrops.

   All four concentrations significantly ($p < 0.05$) reduced intraocular pressure 8 hours after treatment when compared to baseline values. The higher concentrations (0.5% and 0.25%) yielded similar IOP responses which were statistically significantly better than the lowest concentration (0.0625%) while the remaining concentration (0.125%) fell between these.

2. Protocol No. 79-E-10 (Robert A. Stewart, M.D.): Twelve patients with symmetrical ocular hypertension were assessed, in a double-masked fashion for efficacy of Betaxolol 0.5%, 0.25%, 0.125%, and 0.0625%, and placebo to lower intraocular pressure.

All four concentrations of Betaxolol lowered intraocular pressure in a dose dependent fashion. No changes in pulse rate or blood pressure were observed for any concentration. No ocular symptoms were reported.

Controlled Clinical Studies: Betaxolol in several strengths has been studied since June 1980 under 17 different clinical protocols. The safety and efficacy has been evaluated in 1117 patients and normal subjects, exposing a total of 850 people to Betaxolol, 202 to Timolol, and 219 to placebo. Some subjects used more than one medication due to enrollment in multiple protocols or changing test drugs or drug concentrations within a protocol.

1. Protocol No. 79-E-23: Five independent studies compared Betaxolol 0.25% or 0.5% to Timolol 0.5% in a double-masked, randomized fashion. Two of the five studies compared Betaxolol 0.5% as it is planned to be marketed with 0.5% Timolol and are considered by the sponsor to be pivotal studies, and were carried out by Robert H. Stewart, M.D., and Normal S. Levy, M.D.

   Title of both studies: A Double-Masked Comparison of Betaxolol 0.5% and Timolol 0.5%.

   Design of both studies: Randomized, double-masked stuay to compare the safety and relative intraocular pressure (IOP) lowering effect of Betaxolol 0.5% and Timolol 0.5%.

   Details of Robert A. Stewart, M.D. Study:

   40 patients enrolled initially.
   29 patients (15 on Betaxolol and 14 on Timolol) completed the study.

   23 patients (13 on Betaxolol and 10 of Timolol) were ultimately analyzed for IOP reducing efficacy (6 were excluded because of missing data).

   Length of Study: 26 weeks

   2 patients receiving Betaxolol only were dropped from the study for lack of efficacy.
   7 patients (5 Betaxolol and 7 Timolol) were free of other medications that could effect blood pressure and pulse and were suitable for analysis of these variables.

Results of IOP reduction (average of 23 patients):

	Betaxolol 0.5% (N)	Timolol 0.5% (N)
Baseline IOP	28.97 ± 3.52(13)	27.58 ± 0.75(10)
Average Change at:		
Week 1	-6.93 ± 2.59 (13)	-7.23 ± 3.22 (10)
Week 2	-7.74 ± 2.52 (13)	-8.73 ± 2.41 (10)
Week 4	-7.97 ± 2.65 (13)	-9.43 ± 2.48 (7)
Week 6	-7.28 ± 2.40 (13)	-8.53 ± 1.28 (9)
Week 8	-7.63 ± 2.95 (13)	-8.28 ± 2.44 (10)
Week 17	-7.30 ± 3.38 (11)	-8.06 ± 1.94 (9)
Week 26	-5.78 ± 3.78 (13)	-7.38 ± 3.18 (10)

Results of pulse monitoring (7 patients):

	Betaxolol 0.5%	Timolol 0.5%
Baseline pulse rate	76.00 ± 6.16 (5)	81.00 ± 4.24 (2)
Average Change at:		
Week 1	-2.80 ± 10.83	-8.00 ± 5.66
Week 2	0.40 ± 7.67	-8.00 ± 5.66
Week 4	-0.40 ± 8.65	-8.00 ± - (1 patient)
Week 6	-0.80 ± 10.16	-6.00 ± 2.83
Week 8	0.80 ± 7.82	-7.00 ± 1.41
Week 17	-3.60 ± 6.84	-6.00 ± 0.00
Week 26	-2.00 ± 9.70	-5.00 ± 1.41

Summary: Betaxolol 0.5% produced a mean IOP decrease from baseline of 7.5 mmHg compared to an 8.5 mmHg reduction from Timolol which is a statistically insignificant difference ($p > 0.17$). The mean IOP decrease from baseline was statistically significant ($p \ll 0.01$) for both treatment groups at each observation time. Inspection of the pulse rate data shows a lesser pulse rate reduction effect from Betaxolol as compared to Timolol, but the number of subjects was too small to make a statistically valid comparison. No adverse experiences were reported during this study.

Details of Norman S. Levy, M.D., Ph.D. Study:

40 patients enrolled initially
34 patients completed the study (16 treated with Betaxolol and 18 treated with Timolol).
26 patients (12 on Betaxolol and 14 patients on Timolol) received tests solutions only without adjunctive therapy and their data are used for efficacy comparisons.

Length of Study: 26 weeks.

Results of IOP Reduction (average of 26 patients)

	Betaxolol 0.5% (N)	Timolol 0.5% (N)
Baseline IOP	30.63 ± 4.02(12)	28.59 ± 1.93(14)
Average change at:		
Week 1	-9.41 ± 3.65 (11)	-9.84 ± 3.10 (14)
Week 2	-12.30 ± 2.73 (12)	-10.38 ± 2.82 (14)
Week 4	-11.55 ± 3.52 (12)	-10.81 ± 2.75 (14)
Week 6	-11.55 ± 3.18 (12)	-10.52 ± 3.05 (14)
Week 8	-10.55 ± 3.54 (11)	-10.63 ± 2.36 (14)
Week 17	-10.92 ± 2.23 (12)	-10.56 ± 1.61 (14)
Week 26	-10.12 ± 2.74 (10)	-9.55 ± 4.35 (13)

Results of pulse monitoring: As with the Robert H. Stewart, M.D., study, inspection showed a reduction in pulse rate occurring more frequently in Timolol treated patients than in Betaxolol treated patients, but the number of patients was inadequate for statistical analysis.

Ocular tearing, discomfort and photophobia occurred in approximately half of patients from both medications in both studies, but did not necessitate stopping the study medications.

No instances of visual acuity reduction in either study appeared related to the study drugs.

2. Protocol No. C-82-19: A fluorophotometric study of the mechanism of action of ocular pressure lowering by betaxolol was performed, by Richard F. Burbaker, M.D. This study demonstrated suppression of aqueous flow as the mechanism of action responsible for the reduction of intraocular pressure by Betaxolol. Flow rate reductions of 10 to 58% (mean 33%) were observed. Outflow facilities were unaffected by the study medication. The study was a double-masked, randomized trial comparing Betaxolol to placebo in each of 24 normal volunteer subjects. The aqueous flow rate and IOP at the end of the treatment period were found to be significantly lower ($p < 0.01$) in Betaxolol-treated eyes than placebo-treated eyes. There were no significant differences between Betaxolol and placebo eyes for endothelial permeability or anterior chamber volume. No adverse experiences or side effects were observed in any of the 24 study subjects.

3. Protocol No. C-83-19: Betaxolol Duration of Action Study Investigators:

   Alan S. Crandall, M.D., Salt Lake City, Utah
   Normal S. Levy, M.D., Gainsville, Florida
   Ralph H. Weeks, M.D., Fort Worth, Texas
   Robert N. Weinreb, M.D., Dallas, Texas

Study Design: Randomized, double-masked
Study Objective: To determine the ocular hypotensive effect of Betaxolol 0.5% 12 hours after dosing
Number of Subjects: 21 Betaxolol treated patients and 24 placebo treated patients.

Test Schedule: After a washout period, tonometry readings were performed at 8 a.m., 10 a.m., 12 noon, and 10 p.m. on day 1 (baseline). The investigator then instilled one drop of the assigned study medication into each eye after the last baseline reading. IOP measurements were repeated on day 2 for 10, 12, 14, and 24 hour evaluations after drug instillation. Study medications were again administered after the last IOP measurement on day 2. On day 3, final IOP measurements were taken and the study was completed after the 24 hour tonometry reading.

Results: Betaxolol 0.5% treated patients - average of 20.1% reduction in IOP 12 hours following drug installation when compared to baseline ($p < 0.001$).

Placebo treated patients - Average of 5.7% reduction in IOP 12 hours after drop installation.

4. Protocol No. 79-E-11: A Double-Masked Comparison of Betaxolol 0.125% and Placebo.

Investigators:

Ronald L. Radins, M.D.
Robert A. Stewart, M.D.
Mark I. Weiss, M.D.

Study Design: Randomized, double-masked.

Number of Subjects: 21 Betaxolol 0.125% treated
21 placebo treated

Test Schedule: A washout period was followed by 6 weeks of twice daily treatment with Betaxolol 0.125% or placebo.

Results: In two of the three studies (R.L. Radins, M.D., and M.J. Weiss, M.D.), Betaxolol 0.125% produced a statistically significant ($p < 0.05$) greater decrease in IOP than did placebo eyedrops. However, the actual numerical difference of 4 mmHg or less difference between the study drug and placebo would not be clinically useful.

The third study (R.H. Stewart, M.D.) did not demonstrate a clinically significant difference between the two groups.

5. Protocol No. 79-E-11: A Double-Masked Comparison of Betaxolol 0.25% and Placebo.

Investigators:

Delmar L. Caldwell, M.D.
Paul L. Kaufman, M.D.
Edwin N. Keates, M.D.
Norman S. Levy, M.D., Ph.D.
Alan I. Mandell, M.D.
Wayne F. March, M.D.

Study Design: Randomized, double-masked

Number of Subjects: 44 Betaxolol 0.25% treated
47 Placebo treated

Test Schedule: A washout period was followed by baseline IOP measurements and assignment to 0.25% Betaxolol or placebo to be used twice daily for 6 weeks.

Results: During the observation period, the decrease from baseline IOP with 0.25% Betaxolol was greater than that produced by placebo by a statistically significant degree ($p=0.001$). The average actual decline in IOP in 0.25% Betaxolol treated patients was 5.2 mmHg at 1 week and 5.5 mmHg at 6 weeks. Discomfort on instillation was commonly reported for both treatments.

6. Protocol No. 79-E-23: A Double-Masked Comparison of Betaxolol 0.25% and Timolol 0.25%.

Investigators:

David L. Epstein, M.D.
Robert H. Stewart, M.D.
E. Michael Van Buskirk, M.D.

Study Design: Randomized and double-masked.

Number of Subjects: 6 Betaxolol 0.25%
10 Timolol 0.25%
1 Betaxolol 0.25% with adjunctive therapy

Test Schedule: After washout of previous medications and recording of baseline IOP, patients were assigned to one or the other study medications to be used twice daily for 26 weeks. Examinations were scheduled at the end of weeks 1, 2, 4, 6, 8, 17, and 26. Adjunctive therapy could be added as needed to reduce IOP to acceptable levels.

Results: Betaxolol 0.25% - Average IOP reduction - 3.7 to 6.2 mmHg.
Timolol 0.25% - Average IOP reduction - 5.8 to 8.9 mmHg.

The Betaxolol group consistently showed smaller numerical decreases in IOP than the Timolol group, however these differences were statistically significant at weeks 2 and 4 only.

Timolol patients exhibited larger decreases in pulse rate at each observation time than did the Betaxolol group, but the number of patients was too small to determine if this was statistically significant.

Diminished Corneal Sensitivity:

30% of Timolol group
None of Betaxolol group

Ocular discomfort was reported in 5 of 7 Betaxolol treated patients and in 2 of 10 Timolol treated patients. This discomfort was mild and did not persist.

No adverse reactions were reported during this study.

7. Protocol No. 79-E-23: A Double-Masked Comparison of Betaxolol and Timolol: A Report on Patients Who Changed Concentrations.

Investigators:

David L. Epstein, M.D.
Alan I. Mandell, M.D.
Robert L. Stamper, M.D.
Robert H Stewart, M.D.
E. Michael Van Buskirk, M.D.

Study Design: Randomized and double-masked trials to compare the safety and efficacy of Betaxolol and Timolol. The patients started the studies using 0.25% concentrations of both drugs, and then were switched to 0.5% solutions at various times in an unstructured manner. Study duration was 26 weeks.

Number of Subjects: 20 Betaxolol treated
15 Timolol treated

All 35 patients were switched rrom 0.25% solutions to 0.5% solutions in an uncontrolled fashions between the 2nd and 17th week.

Results: Not statistically analyzed.

8. Protocol No. 79-E-23: A Double-Masked Comparison of Betaxolol 0.5% and Timolol 0.5% (combined report).

Investigators:

D.R. Caldwell, M.D.
P.L. Kaufman, Ph.D.
A.L. Mandell, M.D.
R.L. Radius, M.D.
R.L. Stamper, M.D.
E.M. Van Buskirk, M.D.
D.L. Epstein, M.D.
N.S. Levy, M.D.
W.F. Munch, M.D.
M.B. Shields, M.D.
R.A. Stewart, M.D.

Study Design: Randomized and double-masked.

Number of Subjects: 59 Betaxolol treated
71 Timolol treated

The data from 87 additional patients was retained for safety evaluations, but was excluded from efficacy analysis because of the use of adjunctive medications.

Test Drug Schedule: After a washout period, baseline intraocular pressure was recorded, and patients were randomly assigned Betaxolol 0.5% or Timolol 0.5% solution to be used, one drop in each eye, twice daily for 26 weeks. Examinations were scheduled at the end of weeks 1, 2, 4, 6, 8, 17, and 26. Adjunctive therapy could be added at the discretion of the investigator.

Results: Statistical summary of IOP (mmHg) in 130 patients controlled without adjunctive therapy (sponsor's analysis).

Mean ± S.D. (N)

	Betaxolol 0.5%	Timolol 0.5%
Baseline IOP	28.81 ± 3.04(59)	28.59 ± 2.76(71)
Change at:		
Week 1	-7.09 ± 3.35 (54)	-8.68 ± 3.96 (67)
Week 2	-8.15 ± 3.42 (56)	-8.74 ± 3.89 (70)
Week 4	-8.33 ± 3.67 (56)	-9.53 ± 3.46 (66)
Week 6	-8.11 ± 3.66 (56)	-9.09 ± 3.58 (67)
Week 8	-8.30 ± 3.07 (55)	-9.63 ± 3.49 (68)
Week 17	-7.83 ± 3.51 (56)	-9.07 ± 3.43 (69)
Week 26	-6.84 ± 3.75 (56)	-7.65 ± 4.47 (70)

Betaxolol 0.5% as a single medication produced a mean IOP decrease from baseline of 6.8 to 8.3 mmHg over the six month period. The pressure reduction with Timolol ranged from 7.7 to 9.6 mmHg during the same period. Both pressure decreases were statistically significant (p 0.05) for both treatment groups at each observation time, and there was no statistical difference (p 0.05) between the two groups.

Adjunctive therapy was added to the treatment regimen of 34.4% of Betaxolol treated patients and to 25.3% of Timolol treated patients. This difference did not reach statistical significance ($p > 0.20$). In addition, 6 treated with Betaxolol and one patient treated with Timolol were discontinued for lack of efficacy, also a non-significant difference ($p > 0.10$).

Pulse Rate Changes (change from baseline):

Betaxolol: +0.4 to -2.2 beats/min.
Timolol: -3.9 to -5.5 beats/min.

This difference is statistically significant at $p \leq 0.05$.

No difference in mean arterial pressure could be demonstrated between Betaxolol and Timolol treated patients.

Treatment related discomfort was more frequent ($p < 0.01$) in the Betaxolol group than in the Timolol groups. However, no patient stopped either drug because of discomfort, and the magnitude of this problem was not considered great enough to limit the usefulness of either drug.

No adverse experiences were reported for Betaxolol treated patients, while four of seven such reactions reported for Timolol were felt to be treatment related.

SAFETY STUDIES: According to the sponsor, Betaxolol Ophthalmic Solution represents a significant therapeutic advance in the treatment of glaucoma based on its greater safety in patients with cardio-respiratory problems. Timolol, the currently available beta-blocker for the treatment of glaucoma, is a non-selective beta-adrenergic receptor blocking agent. Its use has been associated with severe respiratory and cardiac reactions, and the labeling for Timolol warns against use in patients with bronchial asthma and chronic obstructive pulmonary disease. It states that "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 following administration of TIMOPTIC". Documentation of these respiratory adverse reactions is found in the National Registry of ocular side effects, and in the FDA Drug Bulletin (11/81). Of approximately 600 adverse reactions listed in the 1980/81 National Registry Report, 60 (10%) were pulmonary reactions including one death and, of approximately 300 adverse reactions listed in the 1981/82 National Registry Report, 56 (18%) were pulmonary reactions including nine deaths.

Sponsor's studies (noted below) have shown that Betaxolol HCL (at twice the clinical concentration) and placebo has no significant effect on vital pulmonary function. Inhaled isoproterenol enhances pulmonary capabilities in the presence of Betaxolol HCL 1.0%, but fails to effectively do so after administration of Timolol 0.5%. Clinical use in 29 patients with reactive airway disease has generated 23 patient years of experience without pulmonary complications.

The sponsor feels that the respiratory and cardiovascular advantages provided by Betaxolol Ophthalmic Solution coupled with the fact that its intraocular pressure lowering effects are similar to Timolol, indicates a definite therapeutic advantage for beta-1 blocking agents over non-selective beta-blockers.

1. Protocol No. C-81-25: Betaxolol-Timolol-placebo bronchospasm study in asthmatic bronchitis patients.

   Investigators: Robert B. Schoene, M.D.
   Seattle, Washington

   Study Design: Randomized, double-masked, three-way cross-over in asthmatic patients.

   Patients: Nine patients with a history of obstructive airway disease, who demonstrated at least a 15% decrease in forced expiratory volume in one second (FEV_1), following use of topical Timolol drops, were enrolled into the study.

   Test Drug Schedule: One drop of study medication (1% Betaxolol, 0.5% Timolol, or placebo) instilled in each eye at the beginning of the test session.

   Study medication changed at each new test session.

   Spirometry, respirations, pluse and blood pressure observed for up to four hours following test drug application.

   Beta-stimulant administered by inhalation at the end of observation period with repeat measurements made.

Results:

1. Group mean FEV_1: Values for patients when treated with Timolol were significantly lower than when they were treated with Betaxolol or placebo at 30, 60, 120, 140, and 240 minutes after drug instillation ($p < 0.05$). See Table I.

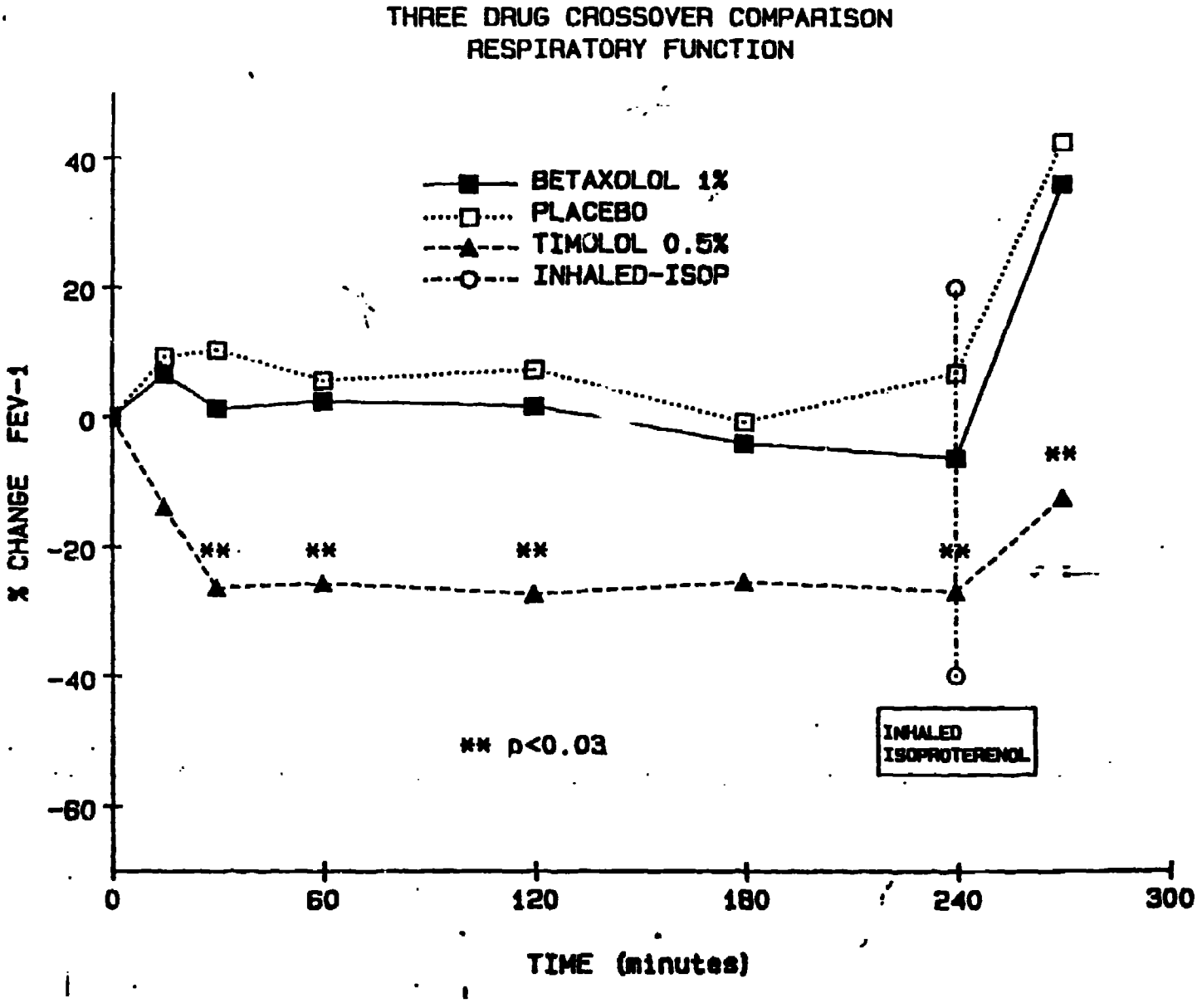
2. Administration of beta-stimulant (isoproterenol): The FEV_1 values for the Betaxolol and placebo treated patients increased to approximately 40% above baseline, but did not return to baseline in Timolol treated patients ($p < 0.05$). See Table I.

3. Respiratory rate: No significant change from any treatment.

4. Blood pressure: No significant change from any treatment.

5. Pulse: No significant differences between treatments for heart rates, as a change from baseline, were detected.

Table I



Adverse Experiences and Side Effects: One adverse experience and seven side-effects were reported during this study. The adverse experience and five of the side-effects (subjective symptoms of wheezing/dyspnea) were reported from the patients while on the Timolol segment of the study. One side-effect each was noted from the Betaxolol and placebo segments of the study. The degree of symptom severity ranged from No Change (4/10), Moderate Increase (1/10), Marked Increase (3/10), and Severe/Life Threatening (2/10) during the Timolol treatment. One patient each from the Betaxolol and placebo treatment groups noted a moderate increase over bseline symptoms (wheezing/dyspnea). Conversely, one patient administered Betaxolol showed improvement over his baseline symptoms. No improvement was observed for the patients during the Timolol or placebo test segments. Two patients were terminated from the Timolol portion of the study by the investigator because of severe life threatening pulmonary distress, patient #13 after 3 hours and patient #19 after 45 minutes. An adverse experience form FD1639 was completed for patient #19. Apart from these predicted cardiopulmonary changes, there were no other side-effects or adverse experiences observed during this study.

Conclusions of the Sponsor: Betaxolol and Timolol are both beta-adrenergic receptor blocking agents but Betaxolol is a selective beta-1 blocker while Timolol is a nonselective beta-1/beta-2 blocker. Therefore, since the respiratory system tissues possess predominantly beta-2 receptors, theoretically, Betaxolol should not exert an effect on the pulmonary system. This proposal, and the previous reports that 0.5% Timolol Ophthalmic Solution can cause potentially dangerous cardiopulmonary side-effects in susceptible individuals (Schoene et al., 1981; Zimmerman et al., 1981) are supported by the results of this study. Although the patients in this study were given twice as much Betaxolol as they were Timolol (quantitatively in terms of mg doses), none of the cardiopulmonary parameters measured was significantly reduced, as compared to placebo, during Betaxolol treatment. Therefore, this suggests that Betaxolol can probably be used safely in patients who have reactive airways disease.

The results of this study also suggest that, once an acute episode of respiratory embarrassment has been precipitated, the patient's response to beta-stimulation is significantly diminished by Timolol treatment. However, this effect was not demonstrated for Betaxolol. This implies that, not only does Timolol bring about significantly greater beta-blockade that does Betaxolol, but that this blockade is so enduring that its reversal by the beta-stimulant is inhibited. This also may be an important safety parameter to be considered in the medical control of asthmatic/bronchitic patients.

2. Protocol No. C-81-25 (Ruben M. Cherniack, M.D.): Originally planned as a randomized, double-masked, three way cross-over study of Betaxolol-Timolol-placebo in asthmatic bronchitis patients, it was amended to eliminate Timolol from the masked portion of the study.

   Nine patients with a history of obstructive and reactive airway disease, and demonstrating at least a 15% decrease in forced expiratory volume in one second (FEV_1) following a challenge with open-label Timolol eyedrops, were enrolled into the study.

The results of the study demonstrated that in patients known to respond to ophthalmic Timolol 0.5% with a significant decrease in pulmonary function, no comparable change occur with 1.0% Betaxolol and none of the pulmonary parameters measured were different with Betaxolol than with placebo.

3. Protocol No. C-81-25 (Woody V. Kageler, M.D.): Two asthmatic patients demonstrating more than a 15% decrease in forced expiratory volume in one second (FEV_1) following use of topical Timolol drops were studied with 1.0% Betaxolol and placebo, and were found not to exhibit any significant change in pulmonary function from either of these medications as compared to Timolol.

Long Term Safety and Efficacy Studies (Open Label): Three hundred and eighty (380) patients on 0.5% Betaxolol Ophthalmic solution twice daily were evaluated over a 36 month period under Protocol Nos.79-E-11L, 79-E-23L, C-82-06, and C-82-13.

Results:

Efficacy: Approximately 65% of the patients' IOPs were controlled with Betaxolol therapy alone with a mean intraocular pressure of 19.2 to 20.7 mmHg. For patients controlled on a regimen of Betaxolol plus adjunctive hypotensive therapy, the mean IOP ranged from 18.5 to 22.8 mmHg.

Safety: Stinging, burning, and tearing upon instillation of the eye drops was observed with an incidence of 30%. Five adverse experiences occurred, only two of which were related to the use of Betaxolol: one case of insomnia, and one of depressive neurosis

Sponsor's Conclusions: While Betaxolol Ophthalmic Solution may produce mild stinging and burning of short duration upon instillation, it is safe and effective therapy for the control of elevated intraocular pressure, either alone or in combination with other adjunctive therapy.

Adjunctive Medications and Compatibility Studies:

1. Protocol No. C-83-30: Betaxolol and Propine (Dipivefrin) (F. Kushner, M.D., R. Ritch, M.D., R. Weinreb, M.D.). This was a randomized, double-masked investigation in which 40 patients using Propine alone had Betaxolol or Timolol added to this therapy for one month.

   Results: Addition of Betaxolol 0.5% or Timolol 0.5% to the study patients' Propine therapy brought about a significant ($p < 0.05$) decrease in IOP compared with Propine alone. Dizziness and headache occurred in one patient in both groups. No adverse experiences were reported.

2. Protocol No. C-83-31: This study to evaluate Betaxolol used concomitantly with Pilocarpine was not carried out because a sufficient number of patients had not been enrolled by the entry cut-off date. This issue is addressed in the long-term evaluation section.

3. Protocol No. C-83-42: Betaxolol in combination with Acetazolamide (J.P. Smith, M.D.): This was a randomized, observer-masked study of 28 patien in which 20 were evaluated for efficacy considerations.

Test Schedule: Patients were randomly assigned to two groups:

Group A: Betaxolol 0.5% twice daily for 3 weeks with Acetazolamide 500 mg in a sustained release capsule twice daily added during the last two weeks.

Group B: Acetazolamide 500 mg twice daily (sustained release capsules) for 3 weeks with Betaxolol 0.5% twice daily added during the final two weeks.

Results (Group A):

1) Betaxolol 0.5% alone reduced the mean IOP from 25.7 mmHg to 21.5 mmHg.

2) The addition of acetazolamide further reduced the mean IOP to 18.2 mmHg.

Results (Group B):

1) Acetazolamide alone reduced the mean IOP from 25.2 mmHg to 18.3 mmHg.

2) The addition of Betaxolol 0.5% further reduced the mean pressure to 17.0 mmHg.

Conclusion: It appears that most of the IOP reduction from combined use of Betaxolol and acetazolamide is from the acetazolamide rather than the Betaxolol.

Summary: A total of 1117 patients or normal subjects were enrolled in 17 studies designed to assess the safety and efficacy of Betaxolol Ophthalmic Solution. Each study included analysis of a combination of ocular and/or systemic safety parameters. Efficacy in terms of intraocular pressure reduction was addressed in most studies. Although several concentrations were evaluated, 0.5% Betaxolol Ophthalmic Solution, the recommended clinical concentration, was investigated in a majority of the protocols.

Normal volunteer studies (three protocols) demonstrated that 0.5% Betaxolol Ophthalmic Solution used twice daily reduces intraocular pressure up to 30%. They also showed that there was no difference from placebo on pulse rate or mean arterial blood pressure.

Dose response studies (two protocols) demonstrated four concentrations of Betaxolol Ophthalmic Solution (0.0625%, 0.125%, 0.25%, and 0.5%) to reduce intraocular pressure in a dose dependent fashion. The 0.5% concentration was noted to be slightly more efficacious than 0.25%, but appeared still to be well within a safe dosage range and was therefore selected as the clinical strength of choice.

Controlled clinical studies (eight protocols) demonstrated the intraocular pressure lowering efficacy of 0.5% Betaxolol to be essentially equivalent to 0.5% Timolol, a drug which, since its introduction in 1978, has become the primary therapy in a majority of glaucoma patients. While Betaxolol 0.5% is somewhat irritating to the eye, as is Timolol, the problem is not serious enough to limit its clinical usefulness. Inspection of several studies revealed a larger magnitude of decrease in pulse rate for Timolol than for Betaxolol, but the number of patients in each study was inadequate to allow statistical comparison.

Two studies conducted under Protocol No. 79-E-23, one by Robert H. Stewart, M.D., and the other by Norman S. Levy, M.D., were considered by the sponsor to be pivotal studies. A total of 49 patients (25 treated with Betaxolol 0.5% and 24 treated with Timolol 0.5%) were evaluated for efficacy. Both drugs produced a significant reduction in intraocular pressure over a six month period, and were statistically equivalent to each other. No adverse experiences were reported from either study.

Safety studies (three protocols) were carried out in 20 asthmatic patients who demonstrated at least a 15% reduction in forced expiratory volume in one second (FEV_1) after receiving topical ophthalmic Timolol 0.5%. None of these patients demonstrated a reduction in FEV_1 from 1.0% Betaxolol Ophtalmic Solution (twice the recommended clinical strength). Statistically this medication did not differ from placebo, and is therefore considered safe for use in asthmatic patients.

Open label-long-term (36 month) safety and efficacy studies were carried out in 380 patients under four protocols. Approximately 65% of the patients had successful control of their intraocular pressure with Betaxolol therapy alone, with the mean IOP ranging from 19.2 to 20.7 mmHg. The remainder were controlled with Betaxolol plus adjunctive therapy with a mean IOP ranging from 18.5 to 22.8 mmHg.

Safety evaluations revealed that stinging and burning upon installation of Betaxolol Ophthalmic Solution may occur in up to 50% of patients, but that this did not limit the drugs clinical usefulness. A total of five (5) adverse experiences were reported, but only two (one case each of insomnia and depressive neurosis) were felt to be related to Betaxolol.

Adjunctive medication compatibility studies (three protocols) indicated that Betaxolol Ophtalmic Solution produces additional significant decrease in intraocular pressure when added to Propine (Dipivefrin) therapy. A small additional pressure reduction of approximately 7% was also noted when Betaxolol was given to patients already receiving Diamox 500 mg sustained release capsules. Studies with Betaxolol added to Pilocarpine therapy could not be carried out due to an inadequate number of patients.

Betaxolol Ophthalmic Solution has been well-tolerated in glaucoma patients wearing hard or soft contact lenses and in aphakic patients. The total cumulative number of patient-years is 15.8, with one patient using Betaxolol for 27 months, and the majority having from 12 to 18 months of experience.

Labeling Review: General labeling claims were reviewed and found to be satisfactory.

Conclusions: These studies adequately support the safety and efficacy of 0.5% Betaxolol Ophthalmic Solution in the treatment of chronic glaucoma either alone or in conjunction with other anti-glaucoma medications.

Additionally, this drug, a beta-1 cardio-selective blocking agent, does not adversely affect pulmonary function in asthmatic patients, which will represent a significant advance in the anti-glaucoma therapy of these patients.

Recommendations: Betaxolol Ophthalmic Solution 0.5% (NDA 19-270), for the treatment of glaucoma, is recommended for approval.

David G. Harper, M.D.

cc: Orig. NDA
HFN-815
HFN-815/CSO/RRLinkous
HFN-340
HFN-815/DGHarper:th/1/4/85
R/D typed 12/12/84
2408b

Addendum:

1. The combined report under protocol No. 79-E-23 (p.10) includes the studies conducted by N.S. Levy, M.D. and R.H. Stewart, M.D., which are discussed in detail on pages 4 thru 6.

2. The 23 patients in the Robert H. Stewart, M.D. study, (p.4) for which efficacy results are tabulated received no adjunctive topical ophthalmic medications.

3. The statement on p.17, "A small additional pressure reduction of approximately 7% was also noted . . .", is in error. The actual reduction was 1 point in 18 (5.5%) and is probably clinically insignificant.

David A. Harper
1-16-85

TT 1/16/85

CHEM
REV

Division of Anti-Infective
Drug Products
Chemist's Review [redacted]
Date Completed: 7/20/84

A.1. NDA 19-270

Sponsor: Alcon Laboratories, Inc.
Fort Worth, Texas 76101

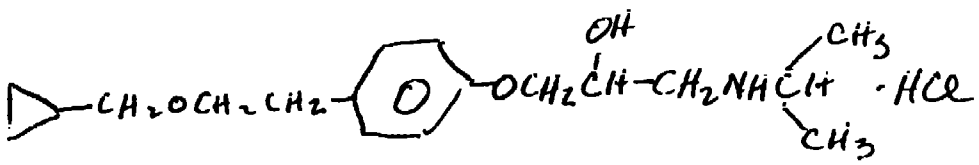
2. Product Names:

USAN: betaxolol hydrochloride
Proprietary: Betaxolol

3. Dosage Form & Route of Administration: 0.5% sterile ophthalmic solution, topical

4. Pharmacological Category and/or Principal Indication: anti-glaucoma agent

5. Structural Formula and Chemical Name(s):



(+)2-propanol,1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]hydrochloride salt

B. 1. Original Submission: 4/26/84 [redacted]

2. Amendments [redacted]

3. DMF Referrals, Related Material: [redacted]

C. Remarks:

This is a new entity previously reviewed [redacted] Apparently neither the sponsor nor the synthetic source have updated their files since 1981 in regard to refining early IND specifications or methods.

[redacted]

D. Conclusions and/or Recommendations:

[redacted]

EIR's will be finalized when the source of the drug substance is clearly defined.

Methods validation is pending.

John Taylor

John W. Taylor, Ph.D.

cc: Orig. NDA
HFN-815 HFN-815/CSO HFN-815/Taylor: gm 7/26/84
HFN-616 R/D Init. by: ARCasola 7/23/84 ARC 8/1/84
1014b

Review Notes NDA 19-270

1&2. Components and Composition

3. Facilities:

a)

b)

4. Personnel: Adequate.

5. Synthesis: Review is deferred pending a response to item 3.

6. Raw Material Controls:

a)

Comments: These specifications are apparently based on the attached lot (Alcon) history. The ranges observed for the specifications were:

b) Other Components: Per USP/NF. Adequate.

7. Other Firms: see item 3.

8. Manufacturing and Processing:

9. Container/Closure:

10. Packaging and Labeling: Adequate.

11. Controls (dosage form):

Comments:

12. Stability Data:
A two year expiry is proposed. The product appears stable at R.T. However, data will be requested to include an analysis of evaporative trend vs. degradation which may be obscured. The turbidity of the product noted at some 35°C and 45°C stations presumably is due to formation of descyclopropyl betaxolol and should be delineated in the other samples or ruled out. See attached brief data summary.

Lot#	Size	av init. assay/BAK assay	av BAK assay	RT assay- wks/BAK assay	350C assay-wks/BAKassay	45oC assay wk/BAK
6234	5ml	104	113	109-130/114.5	111-52/103.5	113-26/103 turbid 4wks, 12 wks
6235	5ml	104	109	107-130/113.5	109-5-52/114.5 s. turbid 26 wks.	106-8/-
6829	5ml	102.5	110.5	105.5-26/113	106-26/121 s. turbid 26 wks	s turbid 4 wk 4wks
6904	10	100	100*	103.5-8/102	105.5-8/104	105.5-4/104 clear all stations
6906	10	100.5	98.5	105-8/106.5	105.5-8/	105.5/106.5 clear all stations

6903 2.5 ml/(5 ml container) data are similar to above lots 6904, 6829

*Outlier discarded by reviewer.

pH data are unremarkable for an unbuffered solution a slight ca 1 pH shift to lower values is noted.

13. Control Numbers: Adequate.

14. Methods Validation:
Requested from one District laboratory and HFN-420 with this review.

15. Labeling:
a) The container and insert require revision in the statement of potency. The potency should be stated as "Each ml contains 0.56 mg betaxolol HCl equivalent to 0.5 mg betaxolol base." The temperature storage limits should be defined.

b) Under "How Supplied" in the insert the storage recommendations, an Rx statement, and a date of printing should be added.

16. Inspections: Requested.

17. Registration: To be determined with item 16.

18. Part 5 Form 356H: Submitted as required.

19. Environmental Impact:
Submitted as required. No impact interpreted at the Bureau level.

PHARM REV

5/3/85

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA

NDA 19-270 (Original Submission, dated 4/27/84)

Date Review Completed: 3/19/85

Applicant: Alcon Labs, Fort Worth, TX

Drug: Trade Name: Not specified.
Generic Name: Betaxolol Hydrochloride
Code Name: SL-75212; ALO-1401

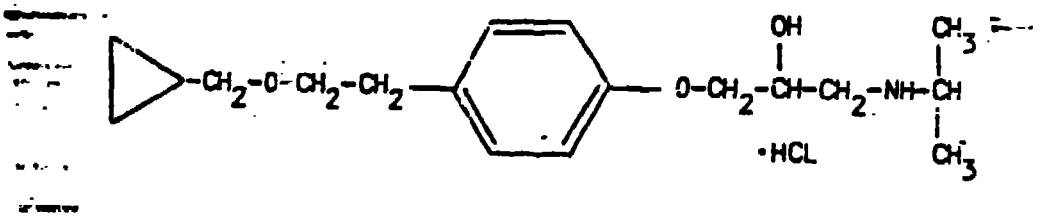
Dosage Form: Ophthalmic Solution, 0.5%

Formulation	Quantity/ml

Chemical Name: (±)-1-[4'-2"-cyclopropylmethoxyethyl)phenoxy]-3-isopropyl-amino-2-propanol hydrochloride

CAS #: 63659-19-8

Chemical Structure:



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

Molecular Wt: 343.9

Category: Beta-adrenergic blocker, topical (ophthalmic)

Proposed Clinical Indication: Glaucoma

Related Submission:

Preclinical Data:

The following animal toxicity studies have been reviewed. Several studies were repeated by a lab different than the original (HRC); therefore, the lab performing the study has been indicated. Unless otherwise noted, all studies employed racemic betaxolol HCl.

List of Submitted Preclinical Studies

Topical Ocular Toxicity - all by Alcon Labs

1. One-day in rabbits
2. One-month topical ocular in rabbits (Ocular histopathology by Experimental Pathology Labs, Herndon, VA)
3. One-month topical ocular (various formulations) in rabbits
4. One-year topical ocular in rabbits

Systemic Toxicity

A. Acute

1. Acute oral in mice & rats (2 studies) - Synthelabo (SL)
2. Acute oral (formulation) in mice - Alcon
3. Acute IV in mice - Alcon

B. Subacute & Chronic

1. 4-week IV in rats - HRC
2. 4-week IV in dogs - Inveresk
3. 4-week oral in rats (3 reports in NDA) - SL, to confirm HRC's findings)
4. 4-week in rabbits - SL (HRC's teratology report)
5. 13-week in F rats - SL (to complement 3- & 6-month HRC studies; see #6)
6. 26-week oral in rats - HRC
7. 61-week oral in rats - Inveresk
8. 26-week oral in dogs - HRC
9. 52-week oral in dogs - Inveresk

Carcinogenicity

1. One-year (dietary) in mice - Inveresk
2. Two-year oral (dietary) in rats - Inveresk

Mutagenicity

A. By Litton Bionetics

1. Ames Test
2. Mouse Lymphoma Forward Mutation

3. Sister chromatic exchange in Chinese hamster ovary cells
4. In vitro transformation of BALB/3T3 cells assay

B By HRC

1. Ames Test
2. Micronucleous test in the mouse

Reproduction

1. Fertility & general reproduction (Segment I) in rats - HRC
2. Perinatal & postnatal in rats (Segment III) - HRC
3. Teratology in rats (Segment II) - HRC
4. Fetal toxicity in rats - SL
5. Teratology in rabbits - HRC
6. Teratology in rabbits - Life Science Research, U.K.

Ocular Pharmacology

1. Pupillary activity in rabbits
2. Corneal sensibility (local anesthesia) in rabbits
3. Intraocular pressure in rabbits

REVIEW OF PRECLINICAL DATA

Note: In this review, Betaxolol will be abbreviated "BTX".

TOPICAL OCULAR TOXICITY (All conducted by Alcon Labs.)

1. One-day Acute Topical Ocular Irritation in Rabbits

Test Material: 0 (vehicle), 0.1, 0.25, 0.5, 1.0 or 2.5% BTX HCl ophthalmic sol'n; Timoptic^{R} 0.5% solution

Treatment: Instilled in the right eye 1 drop (approx. 0.03ml) of test or control sol'n at 20 min. intervals for 6 consec. hrs for a total of 18 treatments. Left eye, untreated (control). Eyes were evaluated at pretreatment and at 6 & 24 hrs after the first dose.

Results: It was concluded that 0.25% & 0.5% BTX HCl ophthalmic sol'n had minimal ocular irritation potential.

2. One-Month Topical Ocular Irritation in Rabbits

Test Materials: 0.25, 0.5, 1.0 or 2.5% BTX HCl ophthalmic sol'ns; ophthalmic vehicle; Timoptic^{R} 0.5% sol'n.

Procedure: 10 rabbits (5/sex)/dose level; instilled 2 drops (approx. 0.06ml) sol'n in the right eye twice/day for 30 consec. days.

Ocular Evaluation: Conjunctiva, cornea, anterior chamber, iris & lens of both eyes examined biomicroscopically (slit lamp) prior to first treatment and weekly thereafter.

Pathology: Eyes & adnexa (Harder's & lacrimal gland) were examined histologically; other tissues examined grossly, but not histologically.

Results: Vehicle control and all treated gps showed slight conjunctival congestion; at 0.5% & 1.0% BTX, the incidence was high on day 8 and low on days 15, 22 & 30. In the 2.5% BTX gp, conjunctival congestion noted on days 8 & 22 was not present on days 15 & 30. Corneal cloudiness was not present in treated or control eyes. Histologically, there was no consistent inflammatory change in the eyes of the BTX-treated gps.

3. One-month Topical Ocular Irritation Evaluation of Various Formulations of 0.5% BTX Ophth. Sol'n in Rabbits (TR 027:3320:0781)

Materials Tested: All 0.5% BTX ophth. sol'ns with the following differences in their composition.:

Group 1. Untreated Control
2. BTX Ophthal. Sol'n (IND formulation)
3. " " " without PO_4 & Tyloxapol (NDA formul'n)
4. " " " without PO_4, Tyloxapol & EDTA
5. Timoptic^R (timolol ophthalmic sol'n)

Objective: To determine whether there were any differences between the sol'n initially used in the IND and that now being proposed in the NDA.

Animals: Total of 50 NZ albino rabbits [10 (5/sex)/group; 5 groups]

Treatment: All rabbits received 2 drops (0.06ml) ophth. sol'n in the right eye, b.i.d. for 30 days (see Table 5, NDA vol. 13, p.26).

Ocular Evaluation: Conjunctival congestion was 0-minimal in gps 1, 3 & 5 and 0-moderate in gps 2 & 4. Conjunctival discharge was 0-minimal in all gps except gp 2, where none was reported. Indirect ophthalmoscopy at pretest (day 3) & terminal (day 30) revealed that optic nerve head, major retinal & choroidal vessels were within normal limits.

Pathology: No gross lesions in any ocular tissues.

Histopathology: (Dr. Ackerman, Experimental Pathology Labs, Herndon, VA.)

Eyes, eyelids, nictating membranes & lacrimal/Harder's glands were examined histologically. No treatment- or drug-related changes occurring only in the treated eyes were reported. The lens & retina in all rabbits were reported to be unremarkable. Microscopic changes noted were considered incidental, occurring in both treated & untreated eyes.

Systemic Effects: No effects on body wt gain. Diarrhea, nasal discharge & alopecia of the perineal area occurred, but none of these effects were drug-treatment-related.

4. One-Year Chronic Topical Ocular Evaluation of BTX Ophthalmic Sol'n in Rabbits (Alcon Labs, TR 065:3320:1280 dated May 1982)

Materials Tested: (a) BTX HCl Ophth. Sol'n, Lot AA1-293; same composition as proposed in the initial IND (PO_4, tyloxapol & EDTA), 0.5% sol'n (b) Timoptic^R (marketed formulation).

Animals: NZ albino rabbits. On the basis of slit lamp & indirect ophthalmoscopy, a total of 108 rabbits were used.

Group	Conc'n	Sac'd	# Rabbits	Approx. # of Treatment Days
Untreated Controls	--	6 month	10	182
		12 month	26 (17)*	365
BTX Ophth. Sol'n	0.5%	6 month	10	182
		12 month	26 (17)*	365
Timoptic^R	0.5%	6 month	10	182
		12 month	26 (19)*	365

*Figures in parenthesis are actual nos. of rabbits subsequent to 2/10/81 randomization.

Note: This study was originally designed to evaluate lower conc'ns of 0.125 & 0.25% and the ophth. vehicle. Due to an outbreak of mucoid enteropathy in the rabbit colony, the latter 3 gps were sac'd, and the sac. schedule was changed from the original 4, 8 & 12 mos. to 6 & 12 mos.

Treatment: Two drops (0.06ml) of the ophth. sol'n were instilled into the right eye of each rabbit; contralateral left eye served as control. Animals were dosed 2x/day for 182 or 365 days. After each instillation, the eyes were manipulated; controls rec'd only eye manipulation.

Ocular Evaluation: By slit lamp exam on day 0 and at 2-wk intervals thereafter. Indirect ophthalmoscopy by vet. ophthalmologist at pretest and termination.

Results:

Pharmacotoxicity

a) Mortality: Six rabbits in both untreated control & Timoptic gps, and 5 rabbits in the BTX ophth. sol'n gp died within the first 2 mos. of the study. Death was not related to drug treatment, but was attributed to mucoid enteropathy confirmed at necropsy & histopathologically. Additionally, death occurring due to other causes (also non-drug-related) are listed in Table 5 of the report and their correlating histopath. causes of death are listed in Table 6 (NDA Vol. 12A, p.57).

b) Body Wts: No stat. sig. difference between any gps.

Ocular Evaluation

a) Slit Lamp Exam: In the BTX ophth. sol'n group:

- minimal-moderate conjunctival congestion at a moderate-high incidence throughout the study

- minimal-moderate conjunctival discharge

- single or very low incidence, during the study, of flare, iritis, corneal cloudiness & corneal neovascularization

b) Indirect Ophthalmoscopy: Optic nerve head, major retinal & choroidal vessels were within normal limits in all gps.

Lens: Since this is an important aspect of the study, the investigator is quoted verbatim:

"In general, moderate-high incidences of numerous 'donut shaped vacuoles' generally along the suture line of the lens, were observed in all groups. These 'vacuoles' were not cataracts as indicated by observations from a board-certified Veterinary Ophthalmologist and histopathologic evaluation. The significance of these vacuoles are not known, as they appear to be a normal finding and possibly age related.

In the untreated Control group (Group 1), Rabbit G388 exhibited a focal deep anterior cortical opacity in the right eye on Day 363; this finding was determined histopathologically to be focal fiber degeneration. Also in this group, Rabbit G345 exhibited a opacity on the posterior capsule in the right eye on Day 363; this finding was determined histopathologically to be focal fiber degeneration. In the Timoptic treated group (Group 6), Rabbit G461 exhibited an opacity in the deep anterior cortex of the lens in the right eye; no lesion was found histopathologically."

Reviewer's Comments: On the basis of lens data (Table 14), this reviewer compiled an incidence table (below) of "abnormal" lenses observed at various times by slit lamp exam.

Group	Day 42	Day 56	Day 181	Day 195	Day 349	Day 363
Untreated Controls	1/30	12/27 (44%)	13/27 (48%)	0/17	1/17	10/17 (59%)
BTX Ophth. Sol'n	0/31	11/29 (38%)	10/26 (38%)	0/17	0/16	12/16 (75%)
Timoptic^{R}	0/30	11/30 (37%)	11/28 (39%)	0/18	0/15	11/15 (73%)

The following points become clear:

- The incidence of "abnormal" lens was nearly equal in all 3 gps (including untreated controls).

- Abnormal lenses did not appear prior to day 42; from days 56-181, the incidence remained high (38-48%); it immediately dropped to zero in all 3 gps on day 195, and remained at or near zero until day 363 when it

again became very high (59-73%). All these data pertain to the treated right eyes; data for the left eyes were not provided.

It should be noted that a scheduled 6-mo. sacrifice was made on day 182, and the possibility cannot be excluded that rabbits with abnormal lenses were selectively killed (although the investigator claims to have randomized these animals).

Day 363 represents the day immediately preceding the final 1-year sacrifice on day 365. It is interesting to note that the incidence jumped from zero (or near zero) on day 349 to 59-75% on day 363.

Histologically, no lesions were noted at 6-mo. sacrifice; at 12-mo. (terminal) sacrifice, lens lesions in one rabbit each were:

- anterior cortical fiber degeneration in (a) rt. eye of untreated control M, and (b) untreated left eye of Timoptic gp M;

- posterior cortical fiber degeneration in rt. eye of untreated control F.

Thus, the lesions seen on slit lamp exam were not apparent histologically.

Pathology: Ocular & non-ocular tissues from each rabbit were examined.

Gross Pathology: (Alcon Labs) There were incidental findings, but no drug-treatment-related lesions were reported.

Histopathology: Performed by Experimental Pathology Labs, Herndon, VA

a) 6-Month Sacrifice: (Report dated 7/24/81):

General pathological cause of death in animals that died or were sac'd in morbund condition is listed in NDA Vol. 12__8, pp. 396 & 397. Most died of mucoid enteropathy.

Ocular: Incidental lesions were detected in the eyes, eyelids, nictating membranes & lacrimal glands. None of these lesions were considered to be treatment-related. The ocular lesions noted were:

- foci of mononuclear cells at the limbus of the cornea;

- foci of mononuclear cells in the submucosal tissues of the nictating membranes of the individual rabbits in the form of lymphoid nodules or as foci of mononuclear cells;

- slight focal to multifocal dilatation of the glandular elements of the lacrimal glands.

b) 12-Month Sacrifice: (Report dated 2/9/82) None of the 4 deaths were drug-treatment-related. (3 Timoptic-treated animals had meningitis due to Encephalitazoon cuniculi infection & 1 BTX-treated animal had scrotal abscess.) No adverse treatment-related changes were reported

in the eyes or other nonocular tissues of any particular organ from rabbits treated with BTX ophth. sol'n when compared to untreated controls.

SYSTEMIC TOXICITY

A. Acute Toxicity

1. Acute Toxicity in Mice & Rats (Synthelabo, 1/23/80)

a) LD_{50} (confidence interval) in mpk were:

	Mice		Rats	
	IV	Oral	IV	Oral
Metoprolol	62(56-69)	1050(766-1438)	78(70-87)	> 1000
Propranolol	38(30-49)	350(250-372)	32(28-37)	510(398-653)
BTX	38(32-44)	920(601-1408)	39(33-46)	1050(945-1166)

b) Material Tested: BTX

Route	Species	LD_{50} (mpk) Male	Female	Clinical Signs
IV	Mice	40 ± 1.15	55 ± 2	tremors, convulsive jumps, clonic convulsions
	Rats	28 ± 1.6	25 ± 1.5	tremors, clonic convulsions
Oral	Mice	350 ± 23	400 ± 30	difficulty in movement, stereotypic behavior, violent clonic convulsions
	Rats	980 ± 95	860 ± 113	*

* Oral - male rats: slight palpebral ptosis, exhaustion, stereotype behavior, hypersalivation, tremor, piloerection, motor difficulties, polypnea, cyanosis

Oral - female rats: loss of motor coordination, protruding eyes, stereotypic behavior, hypersalivation, noisy breathing

2. Acute Oral Toxicity of BTX Ophth. Sol'n in Mice (Alcon)

Test Material: 2.5% BTX HCl ophth. sol'n

Treatment: Single oral admin. of 12.5, 25 or 37.5ml/kg dose of 2.5% sol'n corresponding to 312.5, 625 or 937.5mpk of BTX HCl; volume of sol'n given adjusted to animal wt. Controls received distilled water (not ophth. vehicle).

Results: LD_{50} for BTX HCl = 482.7mpk

3. Acute IV Toxicity in Mice (Alcon)

Test Material: (+) BTX HCl 1.1% (= BTX free base 1%) aq. saline sol'n.

Treatment: Single IV injection of 20, 30, 40 or 50mpk of BTX sol'n further diluted to conc'ns of 0.1, 0.15, 0.2 & 0.25% (+) BTX free base; each received a constant volume @ 20ml/kg.

Results: LD_{50} of BTX free base = 42.6mpk

B. Subacute & Chronic Toxicity

1. 4-Week IV Toxicity in Rats (Huntingdon Research Center, U.K., report BGX 163/167/80791)

Material Tested: BTX

Animals: CD rats of SD strain; 10/sex/group

Groups: Controls; BTX at doses of 2 (LD), 6 (MD) & 15 (HD) mpk/day (expected human exposure: 0.3mg/kg, or 1.5mg/50 kg individual).

Treatment: Rats were injected IV over a period of one minute, once daily for 29-30 days.

Mortality: None

Clinical Signs: None in the LD or MD gps. At the HD, 12 rats (6/sex) showed clinical signs approx. one minute after injection. Most common signs were: unsteady gait & irregular breathing; single instances of piloerection, body tremors & partially closed eyes.

Body Wt & Food Intake: No effect in the LD & MD gps. Reduced food intake resulting in dec. in body wt gain at the HD.

Ophthalmoscopy, Hematology, Blood Chemistry, Urinalysis & Pathology: No drug- or dose-related effects.

2. 4-Week IV Toxicity in Dogs (Report # 1803 dated August, 1980; Inveresk Research International, Musselburgh, Scotland)

Material Tested: BTX (from L.E.R.S.)

Animals: Beagle dogs; 3/sex/dose group

Groups: Saline controls; BTX at dose levels of 1 (LD), 3 (MD) & 6 (HD) mpk (HD gp rec'd 10mpk on day 1, then the dose was reduced due to mortality.) The dogs were injected for 4 wks.

Mortality: 2 dogs died following 10mpk; there were no other deaths.

Clinical Signs: Initially ataxia, salivation, subduedness and a high stepping gait of the hind legs in HD (6 mpk) dogs; severity of these signs disappeared by the middle of wk 3.

Body Wt; Food Intake; Ophthalmoscopy: No treatment-related effects

EKG: Reduced heart rate in the HD dogs after 3 wks

Hematology: No drug-treatment effect reported.

Blood Chemistry: A mild dose-related dec. in GPT after 3 wks of dosing, at which time marginally raised lactate dehydrogenase (LDH) and alpha hydroxybutyric dehydrogenase (HBDH) were also observed in HD animals. However, all values were considered within normal limits by investigators.

Urinalysis; Pathology: No treatment-related effects

3. 4-Week Oral Toxicity in Rats (Synthelabo; Histopathology by Professor J. Dalion; 3 reports in NDA vol. 15, pp. 2-116)

Animals: CD rats of SD strain; 10/sex/gp

Groups	Males	Females
Controls	Controls	Controls
BTX	50mpk	25mpk
"	100mpk	50mpk
"	200mpk	100mpk

The dose was administered by intubation, once daily for 4 wks.

Results

25mpk: No sig. effect at 25mpk in F

50mpk:

- slight inc. in blood glucose
- slight inc. in serum urea (F only)
- Histopathology not done.

100mpk:

- slight inc. in blood glucose
- elevated serum urea; very slight in M, moderate in F
- moderate inc. in serum triglycerides (F only)
- proteinuria slightly greater than in controls (F)
- Histopathology (F only) - no abnormality reported.

200mpk (M only):

- slight inc. in blood glucose
- proteinuria slightly greater than in controls
- Histopathology - no abnormality reported.

4. 4-Week Oral Toxicity in Rabbits (F only): Synthelabo

Objective: In their teratology report, Huntingdon reported occurrence of enteritis & diarrhea in F rabbits at 36mpk/day, PO

Animals: Rabbits HY/Cr/n (Charles River, France); 12 F/group

Groups: untreated controls, vehicle controls & BTX at 30 & 100mpk/day adminstered by gastric intubation, once daily for 4 wks.

Results (Note: no enteritis at 30 or 100mpk dose levels.)

Mortality: 3 HD & 2 LD rabbits died (intubation error)

30mpk: The drug was well tolerated.

100mpk:

- lower rate of body wt gain in beginning, but no stat. difference at the end of the expt.
- moderate inc. in neutrophils
- slight inc. in serum globulin levels

Histopathology: (By Prof. Dalton; done on urinary bladder only.)

- lung lesions due to intubation errors or infection
- urinary bladder normal in all treated animals

5. 13-Week Oral Toxicity in Female Rats (Synthelabo, Paris)

Objectives:

- to complement a similar 3- & 6-month oral toxicity study in rats by Huntingdon Res. Centre (vide infra)
- to study the effects of 400mpk
- to complete dose range at HRC (1.5, 2.5, 25 & 400mpk) by including a dose level of 100mpk
- In a 3-mo. interim report, HRC reported urinary bladder hyperplasia in some animals, inc'd urine volume & inc'd blood urea (F).

Animals: CD-SD rats, F only, starting with 20/gp; in each treated group, 3 rats were lost because of intubation error; 12/gp were examined.

Groups: Controls; BTX at 100 (LD) & 400 (HD) mpk/day

Results

Clinical Symptoms: hypersalivation at both doses

Mortality: 1/17 rats

Body Wt: Slightly retarded at HD

Food & Water Intake: no effect

Renal & Urinary Parameters:

- inc. in blood urea at both dose levels; LD sig., HD marked
- slight inc. in creatinine levels, both doses
- slight inc. in wts of both kidneys (histopath. normal)
- discoloration of renal cortex; rare at LD, somewhat more frequent at HD (histopath. normal)
- slight polyurea at both doses, particularly the HD
- tendency for inc'd no. of epithelial cells & bacteria at the HD
- thickened appearance of the bladder wall in 4/17 rats in LD gp & 7/16 in HD gp (rats not identified)

Histopathology: 12 rats/gp were examined by Prof. Dalton.

- In both dose groups, all urinary bladders were "N.A.O." (no abnormality observed).
- Kidneys were unremarkable at both dose levels.
- Adrenals looked large, but were microscopically normal.

6. 26-Week Oral Toxicity in Rats (Huntingdon Research Centre, Report # BGX/95/78456)

Animals: CD rats of SD strain; 25/sex/group; of these 25, 10 were sacrificed at 13 wks.

Groups: (actually 2 studies)

a) Study # BGX/89, commencing 1/31/77: controls; BTX @ 1.5, 2.5 & 400mpk/day

b) Study # BGX/95, commencing 5/9/77: controls; BTX @ 25mpk

Treatment: Rats were dosed by gavage, once daily, 7 days/wk for 26 wks

Results

Ophthalmoscopy: Indirect ophthalmoscopy at wks 6, 13 & 26 revealed no morphological abnormalities in the eyes of rats at 400 or 25mpk dose.

At 1.5 & 2.5mpk: intermittent salivation immediately after dosing among both M & F lasting approx. 20 min.

At 25mpk:

- From wk 3 on, occasional severe salivation immediately after dosing, lasting for approx. 5 min. in both sexes. From week 13 on, areas of hair loss on and around the face & head in 5 M & 4 F.
- Marginally lowered food intake in F
- Marginally lower water intake in M at wks 5, 11 & 26 and F at wk 26 only, occasionally associated with excretion of lower urine volume.

At 400mpk:

Clinical Signs:

- body tremors & unsteady gait during the first 2 wks of dosing
- salivation following dosing in both sexes
- isolated convulsive episode in 2 rats

Mortality: 6 M & 4 F died

Body Wt Gain & Food Intake: slightly lower

Urinalysis: inc'd output of more dilute urine in F during wks 4 & 12; inc'd urine output during wk 25 by F associated in part with inc'd water intake.

Blood Chemistry: sig inc'd SAP levels in M & F at wks 4, 6, 12 & 25, together with marginally inc'd SGPT levels in M at wk 4; slightly higher plasma urea levels in F at wks 4, 6, 12 & 25, and in M at wks 12 & 25

- sig. dec'd glucose levels in F at wks 25 & 26
- higher K levels in both sexes throughout dosing period

Pathology:

Interim Sacrifice at 13 Wks:

- Higher liver & adrenal wts and marginally higher r. kidney wts were reported in both sexes.

- Microscopic rel. kidney wts in both sexes revealed the following changes:

  - inc'd incidence & extent of aggregations of distended macrophages in the lungs;

  - evidence of possible minor effect on the liver of M characterized by absence of vacuolation in centrilobular hepatocytes;

  - evidence of epithelial hyperplasia of the urinary bladder seen to a moderate extent in 1, and to a minimal extent in 6 F only;

  - evidence of follicular hyperplasia of the thyroid in a proportion of both sexes.

- Final Sacrifice at 26 Wks:

  - higher adrenal wts in both sexes; higher liver, kidney & spleen in both sexes, also uterine wts in F

  - pale subpleural foci in the lungs of 1/10 M & 9/12 F

Histopathology (400mpk Gp): as reported & commented upon by the investigators in rats after 26 wks of dosing:

- Heart: diffuse chronic inflammatory cell infiltration of the myocardium associated with evidence of degeneration of occasional myocardial fibers & deposition of cartilage in the chordae

  tendinae - considered to be associated with indirect pharmacological effect on the CVS

- Urinary Bladder: inc in thickness of the epithelium of the urinary bladder in 4 M and in all 11 sections of bladder seen from F - considered related to drug treatment

- Spleen: engorgement of the red pulp with blood (related to inc'd spleen wt) represents a change in the hemodynamic status of this organ associated with the pharmacological action of the test compound and not, by itself, significant

- Liver: absence of vacuolation of centrilobular hepatocytes in the M and a minimal generalized reduction of fat deposition in both sexes - probably related to an alteration in the metabolism of this tissue, and unlikely to be of toxicological significance

- Kidneys: possible minimal effect in the kidneys characterized by localization of minor tubular changes and associated chronic inflammatory cell infiltration in the juxta-medullary region of the cortex. (The investigators state, "It was considered likely that this effect could represent the early stages of development of specific lesion in this locality in the kidney.)

- Thyroid: reduction of colloid in the follicles of the thyroid glands considered to represent follicular hyperplasia, in a proportion of both M & F. The inc. in incidence & degree of severity at 400mpk, as compared to controls, was considered to be treatment-related.

- Uterus: minimal chronic cell infiltration in the endometrium and minimal hyperplasia of endometrial glands associated with hydrometra and the occurrence of cellular exudate in uterine lumen in a few instances - conformed with inc. in uterine wt and were in some way related to the administration of test compound at 400 mpk. (Ovaries were unremarkable.)

- Adrenals: apparent inc. in size of cells in the zona fasiculata in a proportion of both M & F - consistent with inc'd wt at necropsy.

Reviewer's Comment

a) The applicant has appended to this report a cover letter dated 2/16/81, from David E. Prentice, Principal Pathologist at Huntingdon, with comments in effect saying that "the lesions were minor and of little toxicological importance." (See NDA vol. 16-B, pp. 592-94.)

b) Note that the report of the above 13-wk rat study prompted Synthelabo (manufacturer of the drug) to do a separate experiment at doses of 100 & 400mpk/day in the same strain of F rats concentrating only on the urinary bladder & urine changes (results of the French study were negative; see #5 above).

7. 61-Week Oral (Gavage) Toxicity in Rats (Rpt. # 1839, Nov., 1980; conducted by Inveresk Res. Internatl., Musselburgh, Scotland.)

Note: This study was originally planned for 78 wks, but was terminated prematurely (at 61 wks) due to lesions on hind feet (vide infra).

Animals: Charles River CD rats of SD strain; 20/sex/group

Animal Cages: suspended polypropylene with stainless steel wire grid tops and bedding of white wood shavings (feet in bedding, not on wire mesh).

Groups: Controls (C) - distilled water; BTX at 6 (LD), 25 (MD) or 100 (HD) mpk/day

Dosing: Animals were gavaged via steel cannula daily for 61 wks.

Results

Mortality: A total of 18 rats died 3/20 & 7/20 F in the MD & HD gps; 1/20 M in each of the LD, MD & HD gps; 2/sex in C

Clinical Signs: None attributable to treatment

Body Wt: Dec'd overall body wt gain in M & F of the HD and M of the MD

Food Intake: Slightly reduced in HD M & F. No effect on water intake.

Clinical Lab: 10/sex in the C & HD gps at 6, 13, 26, 52 & 60 wks; MD rats sampled on wk 60

a) Hematology: high reticulocyte counts and mixed total & differential WBC counts in wks 52 & 60 due to foot lesions; no consistent trends

b) Blood Chem.: stat. sig. different from C were: dec'd SGOT & elevated BUN in HD F at wk 52 and elevated SGPT in HD M at wk 60; reduction in triglycerides in M of the HD & MD was not consistent.

c) Urinanalysis: up to 26 wks, no diff. in any gp. HD M in wk 52 started to excrete lower urine vol. (by 50%) with a higher specific gravity; high urine specific gravity in HD F at 60 wks. MD rats at wk 60 showed no effect.

Pathology: Total incidence of neoplastic lesions tabulated (non-neoplastic lesions were not - for these, see data for individual rats). The investigator states, "No lesions were seen either macroscopically or microscopically which could be attributed to dosing with SL 75212 (BTX). Lesions which are expected findings in rats of this age were however found, examples being bile duct hyperplasia, pituitary adenoma & chronic glomerulonephropathy (CGN)..."

Reviewer's Comment: Inspection of lesions in the individual rats did not show any lesions in the urinary bladder.

Lesions in the Hind Feet: It should be noted that the rats were housed in plastic cages with bedding (feet not exposed to wire mesh) and the lesions occurred only in hind feet. The lesions described as swollen and/or ulcerated hind paws and its incidence is tabulated below.

Sex	Males				Females			
Group	1	2	3	4	1	2	3	4
No. of animals with hind foot lesions	13	18	12	15	19	13	18	10
Week of first observations of hind foot lesions	28	28	28	28	27	27	27	21*

* This was one single animal; other animals in this group showed hind foot lesions from week 27 onwards.

The investigator states:

"Many rats had lesions of the hind feet (see page 16 for incidence) which produced several related histopathological changes. In these cases lymph node hyperplasia, splenic white pulp hyperplasia and haemosiderosis, bone marrow hyperplasia and extramedullary haemopoisesis were commonly found and are not commented on in individual reports unless gross findings require comment or the condition was extreme. The term reactive hyperplasia is used to describe lymph node morphology in association with these foot lesions and indicates a normal proliferative response to chronic infection It does not imply progression to a more severe lesion such as neoplasia, although occasional neoplastic lesions were found."

8. 26-Week Oral Toxicity in Dogs (Huntingdon, Rept. # BGX 88/77881 dated 11/30/77)

Animals: Pure-bred beagles; 5/sex/dose group (2/sex/gp were sac'd in the 13th week)

Groups: Controls (C) - empty gelatin caps; BTX @ 2 (LD), 6 (MD) & 20 (HD) mpk/day

Treatment: Dogs were dosed orally (gelatin caps), once daily, 7 days/week for 26 wks.

Results

Mortality: One C-F was killed

Clinical Signs:

- Convulsions, accompanied by "limb-paddling" movements, involuntary jaw snapping, arching of the back & excessive salivation were seen on isolated occasions in 1 MD & 1 HD dogs.

- "Head-nodding" - seen in 2 HD dogs, usually within 2 hrs of dosing.

- Vomiting, occasionally seen in several dogs from all gps, up to 140 minutes post-dosing. The greatest incidence was in the HD gp.

- Salivation, seen in 2 HD dogs before & after dosing. This sign was not seen from wk 19 on.

- One MD dog appeared subdued on day 16. The heart sounded arrhythmic on auscultation; this was confirmed by ECG. The pulse was weak & thready and the HR was low. Complete recovery ensued by 2 days later.

Ophthalmic Exam: Performed once pretest, then after dosing on wks 4, 8, 12, 17, 21 & 25. Consisting of the Schirmer tear test in the unanesthetized and anesthetized right eye. Slit lamp after 25 wks of dosing; prior to slip lamp corneas were stained with sodium fluorescein.

- Schirmer tear test - During dosing, the HD gp tended to show a reduction in lacrimal secretion when compared to C. On most occasions, this achieved stat. sig. The reduction for this gp, however, was not progressive. Occasionally, sig. reductions were seen for the remaining treated gps.

- Ophthalmnoscopy - From wk 21, there was an apparent dose-related inc. in incidence of dogs showing minor corneal damage, lack of corneal lustre & photophobia. These signs were considered a manifestation of the pharmacological activity of BTX.

- Slit lamp exam - This was performed during wk 26. Exam revealed moderate or severe punctate epithelial erosion in 1 C & 4 HD dogs. Minimal punctate epithelial erosion was seen in all gps.

Commenting on the ocular findings in the dogs (vide supra), Dr. Heywood of H.R.C. (NDA vol. 17, pp. 351-353) remarked:

- Clinical exam indicated that repeated insertion of Schirmer test papers induced minor corneal damage which reversed within 24 hrs.

- Punctate epithelial erosions (seen in majority of dogs including C) "are not considered to be findings of major clinical importance."

- In the dog, the Schirmer test measures tears produced by irritation and which can be modified by local anesthetic.

- Schirmer tear test values of less than 9mm/min. accompanied by ocular irritation are considered suggestive of keratoconjunctivitis sicca when induced chemically. Reduction in tear secretion in HD dogs was detectable after 4 wks, continuing to wk 21. There was no evidence to suggest that this reduction was progressive; furthermore, using the standard test in unanesthetized state, readings below 9mm/min. were never recorded.

- Histologically, lesions in the lacrimal gland were noted. The replacement of glandular acini in some lobules of the lacrimal glands with adipose tissue is a minor change and of doubtful pathological sig. In the absence of morphological change in the glandular epithelium, this change cannot be interpreted as indicating a treatment-related atrophy.

- The inhibition of lacrimal gland secretion following the HD level admin. of beta-blocking agents is interpreted as a pharmacological effect and a manifestation of toxicity.

9. 52-Week Oral Toxicity in Dogs (Rpt. # 1497 dated August, 1980; conducted by Inveresk Res. Int'l., Jan. 1979 to Jan. 1980)

Material Tested: BTX

Animals: Beagle dogs; 4/sex/group

Groups: Controls (empty gelatin caps); BTX @ 2 (LD), 6 (MD) & 20 (HD) mpk/day

Treatment: All dogs were dosed orally (gelatin caps containing test material) prior to feeding at ca. 10 AM each day, 7 days/wk for 52 wks.

Results

Mortality: One HD dog died 2 hrs after dosing on day 4; no obvious cause of death. This dog was replaced.

Clinical Signs: "Head nodding" movement, a tendency for a high stepping gait, occasional vomiting and in some cases, whining after dosing. Such signs developed within 1 hr of dosing, then subsided over the following 4 hrs. These signs were dose-related in intensity and were seen in dogs at the MD & HD in the first 2 wks of dosing, and thereafter, only in the HD dogs up to wk 6.

Body Wt., Food & Water Intake: No treatment-related changes

Ocular Exam: Indirect ophthalmoscopy & Schirmer tear test were performed at pretest and during wks 6, 12, 24, 38 & 50 of dosing. No treatment-related effects were reported on ophthalmoscopy. Group mean values of tear test, i.e. lacrimal secretion rate (mm/min.) per group are tabulated in NDA vol. 18, p. 27.

At wk 24, reduction in secretion values in the HD gp (20mpk), though stat. sig. (P less than 0.01), was attributed to difference in individual values and was not considered biologically sig. by the investigators. (Histologically no abnormality was reported in the lacrimal gland of the HD gp.)

EKG's & BP: Performed at pretest and wks 6, 12, 24, 38 & 50; lowering of HR in the HD dogs in the 2nd half of the study; slight dec. in systolic BP in MD & HD dogs

Lab Investigations: (Pretest and during wks 6, 12, 24, 39 & 51)

Hematology: No consistent adverse effects reported.

Blood Chemistry: Elevated BUN in HD dogs during the later stages of the study.

Urinalysis: No treatment-related effect were reported.

Organ Wt: No treatment-related changes reported.

Gross & Histopathology: No evidence of any obvious direct toxicological effect due to treatment with BTX

CARCINOGENICITY

1. Carcinogenicity in Mice following Oral (diet) Admin. for 102 Wks: (Rpt. # 2235 dated Jan. 1982; Inveresk Res. Int'l., March 1979 to March 1981)

Material Tested: BTX mixed in the diet (ppm conc'n) to provide the scheduled dose (mg/kg/day). Test diets prepared once/wk for the first 26 wks, and once/2 wks thereafter.

Animals: CD-1 Swiss mice from Charles River Labs, Margate, Kent, U.K.; 4 wks old, 18-20 g in wt; 50/sex/gp

Groups:	Dose (mpk/day)	Conc'n in Diet** (ppm)	Animal Numbers* Males	Females
Controls	0 (C)	0	201-205	451-500
"	0	0	251-300	510-550
BTX	6 (LD)	39-58	301-350	551-600
"	20 (MD)	128-179	351-400	601-650
"	60 (HD)	389-564	401-450	651-700

*Started from 201 (i.e. mice below this number not used).
**Dietary conc'n of BTX varied due to inc'd wt of the mice.

Selection of Dosage: The doses were based on the results of a 28-day preliminary study. The HD was the max. tolerated dose (MTD); the LD was 1/10 the MTD; the MD was the log. mean of the low & high doses.

Food Intake: Quantity consumed (including food scattered) by each animal was calculated once/wk, commencing one week pretest, once/wk up to wk 26, and at 2-wk intervals thereafter.

Duration: BTX dietary admix was fed to mice for 102 wks & 3 days. (The study was originally planned for 78 wks.)

Results

Mortality: A total of 305 mice died spontaneously or were killed in extremis. No dose-related trend was observed.

Clinical Signs: none which could be attributed to treatment

Body Wt:

- Males: reduction in wt gain at the HD from wk 34 on was stat. sig. different from C in wks 38, 78, 90 & 102; no treatment-related effect in LD or MD

- Females: reduction in gain at the HD from wk 30 on; stat. sig. different from C, wks 38, 66 & 78; LD & MD not affected

Food & Water Intake: no treatment-related effect

Pathology: All animals which died spontaneously [termed "premature decedents" (PD)] or were killed in extremis (KIE) or at termination as terminal kill (TK) were autopsied. Autopsy is defined as external exam, including body orifices and exam & fixation of tissues (see NDA vol. 19, pp. 19-21). Tissues included 3 cross-sections from the brain; eyes were examined histologically only if abnormal on gross exam.

Reviewer's Comments: To distinguish various histologic lesions, e.g. hyperplasia and/or neoplasia, and to further distinguish benign & malignant according to investigators' terminology, this reviewer has tabulated (see appended tables) in condensed form, incidence & histomorphology in both M & F.

Non-neoplastic Lesions: These included chronic nephropathy, chronic hepatitis, cardiomyopathy, interstitial pneumonitis & amylodosis - all considered to be due to aging of the mice.

Neoplastic Lesions: No sig. dose-related patterns in tumor incidence were identified. Please see statistical analysis (vide infra).

Statistical Analysis: The following is the summary of effects that were sig. at 95% confidence level:

- Males: reduced mortality at the LD only

- Females: reduced incidence of definitely malignant lung tumors at the LD dose only; reduced incidence of malignant tumors of any site at the LD only

- Sexes Combined: reduced mortality at the LD only; reduced incidence of tumors of other sites (as listed in Table 12), at the MD only; reduced incidence of malignant tumors of any site at the LD only

Of these effects, those relating to survival and total malignant tumor incidence are most likely to represent a true biological effect, as the significance was not only highest for both sexes combined (P less than 0.01 for survival & P ca. 0.01 for total malignant tumor incidence), but a similar pattern was seen in both sexes, though it should be realized that these effects were only seen at the LD level.

The treatment showed no evidence of sig. increase of tumor incidence at the 95% conf. level. The only site worthy of any comment in this respect seems to be the uterus, where there was an excess incidence at the HD level for both vascular & non-vascular tumors. However, bearing in mind the weak level of sig. (only 90% conf. level and only in some comparisons), the lack of effect seen at the other dose levels, and the likelihood of chance "significant" findings due to the multiple comparisons problem, there seems no reason to suspect a real effect from these data.

Note: Please see tabulated data for this study in Appendices I-V, attached to this review.

2. 2-Year Oral (dietary admix) Carcinogenicity Study in Rats (Rpt. # 2076 dated Aug. 1981; Inveresk Res. Int'l)

Material Tested: SL 75212-10 in the diet

Animals: Sprague-Dawley rats (Charles River Labs, U.K.); ca. 4 wks old and 80-90 g in wt; 50/sex/dose gp

Housing: Rats housed singly in suspended polypropylene cages with stainless steel wire grid tops & bottoms.

Groups:	Dose (mpk/day)	Conc'n in Diet* (ppm) Males	Conc'n in Diet* (ppm) Females	Animal Nos. Males	Animal Nos. Females
Controls (C),	0	0	0	1-50	251-300
untreated	0	0	0	51-100	301-350
BTX LD	3	25-72	25-53	101-150	351-400
" MD	12	101-289	99-220	151-200	400-450
" HD	48	404-1108	398-817	201-250	451-500

*Conc'n of BTX varied because of increase in body wt (less in the beginning and more at termination).

Treatment: Test compound was fed in the diet for 104 wks.

Basis for Dosage: In preliminary test, 10/sex rats 4-5 wks old were fed diet containing BTX so that they consumed @ 48 mpk/day. This was done solely to detect any palatability problems for the main study.

Results

Mortality: Total of 311 rats died (or were killed in extremis) prior to termination. Slightly fewer deaths in the HD gp than in C.

Clinical Signs: Many rats developed sore hind feet which sometimes progressed to large ulcerated lesions. The condition occurred in all gps with approx. equal severity. No other effects attributable to treatment.

Body Wt: M & F at the LD & MD consistently showed similar or slightly greater body wt gain than in C, but the difference rarely achieved stat. sig. HD rats showed consistently reduced body wt gain when compared to C, beginning approx. wk 7. This reduction became highly stat. sig. in M from wk 21 and in F from wk 9.

Food Intake: No sig. gp differences at any point in the study. Rats of the HD gp showed a "marginal" reduction in food intake when compared to C over the first 52 wks of the study. Quoting Ross et al.*, the investigators state that reduced mortality in HD M was related to the lower mean body wt of this gp.

*Ross et al. Lasting influence of early calorific restriction on the prevalence of neoplasms in the rat. JNCI 47: 1095-1113, 1971.

Pathology:

Males:

Neoplastic Lesions: Two stat. sig. changes were (a) decreased no. of pheochromocytomas at the LD and (b) presence of SC lipoma in 4/50 rats at the MD, but not in the LD or HD.

Tumors occurring only in treated rats showed random distribution and low incidence, thus indicating they were unrelated to drug treatment. This includes 2 SC anaplastic sarcomas in MD & HD rats that died prior to termination; their distribution was not stat. sig.

No significant dose-related patterns in the incidence of total no. of animals with benign, malignant, multiple or metastatic tumors.

Non-neoplastic Lesions: These included chronic nephropathy, periarteritis & degenerative lesions of the adrenals which were typical of aging rats. Also noted was chronic ulcerative dermitiitis probably of bacterial origin. None of these were compound-related in incidence or severity.

Females:

Neoplastic Lesions: In the HD gp, there was a slight increase in clear-cell carcinomas of the thyroid & pituitary adenomas plus decrease in pituitary carcinomas.

Among the tumors occurring only in treated rats, their random distribution and low incidence (usually single instances) showed these to be not related to treatment.

A total of 6 rats (1 LD; 4 MD; 1 HD) had hepatic neoplastic lesions, but they were not present in a dose-related pattern.

There was no sig. dose-related changes in the total no. of animals with benign, malignant or metastatic tumors. However, in the MD gp there was a stat. sig. increase in no. of rats with multiple (more than one type) tumors among those rats dying prior to termination. As this inc. was not seen in terminal rats of this gp or in the LD or HD gp, it was thought by the investigators to be unrelated to treatment.

There were no sig. intergroup trends in the latency period for each type of tumor.

Non-neoplastic Lesions: Similar to those mentioned for the M. Chronic ulcerative dermatitis of the hind foot pads occurred more in F than in M. Non-neoplastic lesions occurring only in treated rats were present in small nos. and according to investigators, were of minor importance; they could not be related to BTX.

Note: Incidence of various lesions observed histopathologically can be found in Table 6 (males) & Table 11 (F). For definition and interpretation of terminology used in histopathology, please see pp. 17-18 of the report (NDA vol. 21, pp. 23-25).

Statistical Analysis: (NDA Vol. 22, pp. 573-613): The following summary listed effects which were stat. sig. at at least at 95% confidence level:

Males:

- dose-related reduced mortality in treated animals, particularly marked at the HD
- dose-related reduced pituitary tumor incidence in treated animals particularly marked at the HD

Females:

- inc'd skin tumor incidence at the LD only
- inc'd adrenal medullary tumor incidence at the MD only
- inc'd liver tumor incidence at the MD only

Sexes Combined:

- dose-related reduction in mortality in treated animals, marked at the HD
- reduced pituatary tumor incidence in treated animals, most marked at the HD, but also sig. at the LD
- reduced thyroid follicular tumor incidence, evident only at the LD
- inc'd incidence of malignant skin tumors evident at the MD

Of these effects, those related to the skin, thyroid, adrenal medulla & liver were all of marginal sig. at the 95% conf. level, and evident only in one sex and at one (intermediate) dose level. The effect on survival & pituitary tumor incidence seen in M, on the other hand, are far more likely to represent true biological effects, since they have a much higher level of statis. sig. and show a dose-related trend.

Note: Please see tabulated data for this study in Appendix VI, attached to this review.

REPRODUCTION

1. Fertility & General Reproductive Performance in Rats (Huntingdon Res. Centre: Rpt. No. BGX 112/79661 dated 9/19/79)

Animals: CD Sprague Dawley rats (Charles River Labs); 15 M & 30 F/gp

Groups: Controls (C); BTX @ 4 (LD), 32 (MD) & 256 (HD) mpk/day, orally by gavage

Treatment: M - 9 wks prior to mating, continued during mating period;
F - 20 wks prior to mating, continued during mating period.

Procedure: For mating, 1 M + 2 F were caged together; daily vaginal smears were taken for a max. of 20 days (mating period); 11-14 F/gp were sac'd on day 20 of pregnancy, remaining F gave birth and reared their pups.

At weaning, 12/sex/gp in C, LD & MD gps were selected to assess reproductive performance in the F-1 generation. These animals were not dosed, but were exposed in utero. Pups from the HD gp were not selected because of the adverse toxic effects this dose had on the F-0 animals.

Results

a) F-0 Parents (dosed M & F)

Male Fertility: Mating performance & pregnancy rates were comparable for all gps, indicating no effect on M fertility.

Female Fertility:

HD:

- clinical toxic signs, e.g., salivation at post-dosing
- 5/30 F died, mostly during pregnancy or early lactation
- highly sig. inc. in incidence of embryonic/fetal deaths resulting in reduced litter size & reduced mean fetal wt on day 20 of gest.
- highly sig. inc. in neonatal pup mortality, including total loss of 6/11 litters, leading to sig. reduction in litter size & reduced mean pup wt attaining max. divergence from C at day 8 post-partum
- correlating with lower mean pup wt of survivors, mean ages of development of pinna unfolding, righting reflex, startle response, second coat growth & eye opening of F-1 offspring; because of their fewer nos., no meaningful comparison with C

- MD
  - transient clinical toxic signs (salivation)
  - sig. lower litter wt & slightly lower mean fetal wt on day 20 of gest. correlating with slightly lower litter wt & sig. lower mean pup wt at birth & day 4 post-partum
  - marginal delays in the mean age of development of startle response & vaginal opening - may or may not be relevant

LD: slightly lower mean fetal wt & sig. lower litter wt on day 20 of gest. followed a dose-related pattern seen at the higher doses of 32 or 256mpk

b) F-1 Generation: no obvious effect on growth to maturity, mating performance, pregnancy rate, litter data at day 20 of gest. (F) or performance in behavior tests

2. Effect of BTX on Pregnancy of the Rat (Segment II Teratology) (Huntingdon Res. Centre, Rpt. No. BGX 111/78296 dated 10/16/78)

Animals: CD rats (presumably a SD-derived strain); 20 pregnant F/gp

Procedure: Controls (C); BTX @ 4 (LD), 40 (MD) & 400 (HD) mpk/day orally by gavage from days 6-18 of pregnancy. Rats were killed on day 20 of pregnancy & evaluated for visceral & skeletal anomalies.

Results

HD:

- Clinical signs post-dosing: Body wt was severely retarded and at termination was sig. lower.

- sig. inc'd incidence of late embryonic deaths leading to sig. inc'd post-implantation loss & lower viable litter size; mean litter wts & mean fetal wts sig. reduced

- Correlating with the reduction in fetal wt, there was a high incidence of fetuses showing varying degrees of visceral & skeletal changes, most of which appeared to be the consequence of a marked general retardation of development. According to the investigators, "even the occasional frank malformations observed (e.g., cleft palate in 3 fetuses) could be considered an extension of this general retardation."

LD & MD: Clinical signs (salivation) at post-dosing was seen in the MD F, but no other maternal effects. Values for litter size, post-implantation loss, litter & mean fetal wts were comparable with C.

3. Fetal Toxicity in the Rat (Segment II Teratology)
(Synthelabo Report No. B.0102.81.020; no date, no GLP statement)

Animals: CD-SD rats (Charles River Labs, France)

Experimental: (Two experiments done.)

Group	Dose (mpk/day)	No. of Animals Expt. I	Expt. II	Total
Controls	0 (C)	15	12	27
BTX (base)	10 (LD)	0	20	20
"	200 (MD)	15	12	27
"	400 (HD)	15	0	15

Treatment: Rats were dosed orally (intubation), days 6-15 of pregnancy; in the HD gp, treatment was stopped on day 13 rather than day 15 (presumably due to maternal toxicity). All rats were sac'd on day 20 of gestation and evaluated for fetal anomalies.

Results

Maternal Toxicity

- Clinical Signs: marked lethargy in HD gp

- 7/13 HD rats died; on autopsy, gastric erosions in 2 rats

- Body Wt Gain: LD, normal; MD, markedly less; HD, marked inhibition

Reproductive Parameters:

Embryotoxicity:

- No. of live fetuses were normal in LD gp & slightly dec'd in MD gp; all fetuses in 5/5 pregnant F died (post-implantation) in HD gp; slightly inc'd post-implantation losses in MD gp

- Preimplantation losses & mean fetal wts at the LD were not affected.

Teratogenicity: External Exam: no abnormality at the LD & MD; total resorption at the HD

Visceral Exam: (C & MD; brain sections not examined; 2/3 fetuses in Expt. II only) No malformations occurred. Delayed ossification and extra ribs occurred with about equal frequency in C & MD gp.

4. Effect of BTX on Pregnancy in the NZ White Rabbit (Segment II) (Huntingdon Res. Centre Rpt. # BGX 110/79548 dated 2/14/80)

Preliminary Study: BTX was administered orally (gavage) at dose levels of 36, 100, 200 & 300mpk/day, days 1-13 in nonpregnant does. Doses of 200 & 300mpk were associated with death, anorexia, wt loss, hunched posture, lethargy, ptosis, unsteadiness, occasional body tremors & collapse. Treatment with 100mpk was associated with initial wt loss, hypersensitivity, hunched posture, lethargy & occasional unsteadiness; no marked conclusive effects at 36mpk.

Main Study: BTX was administered at 4 (LD), 12 (MD) & 36 (HD) mpk/day orally (gavage) to pregnant rabbits, day 2-18 of gestation; controls (C) rec'd distilled water. All rabbits were killed on day 29 of gestation, necropsied, and evaluated for teratologic parameters.

Results

- Approx. 30% rabbits in each drug-treated gp died due to enteric disorder; 5% mortality in controls.

- Pregnancy rate, as assessed by no. of pregnant animals & pre-implantation losses, was not adversely affected.

- Among the healthy surviving pregnant rabbits, further litters were lost due to total resorptions and/or abortions; incidence was 0, 14, 8 & 57% in C, LD, MD & HD dams, respectively. Alternatively, deaths & exclusions (except those due to non-enteric causes) total litter losses might be combined to provide incidence of pregnant dams failing to maintain pregnancy (termed as "pregnancy failure"). The incidences were: 7, 37, 42 & 67% in C, LD, MD & HD gps, respectively. These data indicate the effects of treatment, though greatest at the HD, may also have been induced at the LD & MD.

Note: The investigator stated that adverse effects on pregnancy (total litter losses) were also observed in concurrent Segment II & III reproduction studies in the rat at doses of 256 or 400mpk.

- Assessment of effects on litter values was limited by the high incidence of deaths, exclusion & total litter loss. Within these limitations, treatment at all doses was associated with inc'd post-implantation loss mainly associated with inc'd incidence of late embryonic deaths and/or abortions.

- Consequent to the inc'd post-implantation loss, litter size & litter wts were reduced compared to C. These differences were marginal at the LD, minimal at the MD & marked at the HD.

- Within the limitations (vide supra), there were no sufficiently remarkable differences in incidence of major malformations, minor anomalies or skeletal variants to indicate specific effect of treatment on embryonic & fetal development.

5. Effects of Oral Administration upon Pregnancy in the Rabbit (Rpt. # 80.LES.024.049 dated 2/27/80, Life Science Research, Stock, Essex, England)

Procedure: NZ white rabbits were artificially inseminated using pooled semen from proven M, followed by 50 i.u. of LH (Pregnyl, Organon Labs) injected IV to ensure ovulation. Estrus had been synchronized in these F by LH treatment 3 wks previously.

Groups	Dosage (mpk/day)	Post-implant Loss (%)	# Dams per Gp	# Aborted
1. Controls	0	15.4	14	0
2. BTX	1	3.4	14	0
3. "	4	3.0	14	1 (day 23)[a]
4. "	12	10.6	18	1 (day 26)
5. "	36	50.4	18	2 (day 26)[b]
6. Controls*	0		4	0
7. BTX*	4		4	1 (day 19)

*Used for pharmacokinetic study.

[a] emaciated
[b] 1 total litter loss + 1 abortion

All rabbits were dosed orally by gavage once daily, days 6-18 of pregnancy. All animals were killed on day 29 of gestation and evaluated for reproductive & teratologic parameters.

Results

Maternal Effects: One control & one HD rabbits died due to respiratory tract infection or tracheal intubation. Body wts were unaffected. There was no consistent treatment-related change in food & water intake.

Abortion & Total Litter Loss: One F each in Gps 3, 4 & 7 aborted and one had total resorption (see NDA, vol. 23, p. 340, Table 6).

Litter Data:

Pre-implantation Loss: No dose-related effect.

Post-implantation Loss: Stat. sig. (P less than 0.05) increase in HD F (36mpk); this was associated with dec'd live litter & increased fetal & placental wts. Based on all animals that survived to term and bore evidence of implantation, post-implant losses were 15.4, 3.4, 3, 10.6 & 50.4% in groups 1 thru 5, respectively.

However, if the mean values were derived from animals which survived to term and bore viable pups, the value for HD F was 45.5%, still stat. sig. (P less than 0.05), indicating that effects were indeed real at 36mpk. Mean post-implantation losses in other dose gps were within the concurrent control values; mean values in their historical control data ranged from 7.6-15.4 (see NDA vol. 23, p. 341-342, Tables 7 & 8).

Fetal Morphology: No indication of any drug- or dose-related effects.

Reviewer's Comments: From both rabbit studies, it is clear that stat. sig. post-implant. losses were noted in rabbits at 36mpk. Post-implant. losses were also noted in the rats at 400 (but not at 40) mpk.

6. Peri- & Post-Natal Development in the Rat (Segment III)
(Huntingdon, Rpt. # BGX 113/79580 dated 10/9/79)

Animals: CD-SD rats (Charles River Labs) 20 timed-pregnant F/group

Treatment: Controls; BTX at 4, 32 & 256mpk/day orally (gavage), from day 15 of gestation to day 21 post-partum

Parameters Observed: Treated parent animal (F-0) & litter (F-1) values from birth to lactation to weaning were monitored for growth & development of F-1 offspring to weaning; selected F-1 offspring were reared to maturity, and their growth, performance in specific behavior tests, and reproductive capacity assessed.

Results

4 & 32mpk: In F-0 parents, clinical signs of the drug (inc'd salivation & piloerection) at 32mpk were noted, but no other adverse effects were noted in the treated parents. Also, there were no conclusive adverse effects on the fetuses (F-1 progeny).

256mpk:

- F-0 Dams: The effects were indicative of maternal toxicity, e.g., toxic signs, reduced body wt gain, high incidence (79%) of total litter loss occurring perinatally or immediately postnatally.

- F-1 Progeny: Among the few surviving litters, inc'd pup mortality & reduced mean pup wt during the first 4 days post-partum with consequent

reduced litter size & wt and pup wt thru lactation to weaning; slightly delayed mean age of development of startle response & full coat growth.

There was lower body wt gain, slightly delayed mating, slightly lower pregnancy rate, and slightly lower no. of corpora lutea & implantations/litter among the selected F-1 reared to maturity. These differences were considered to be a consequence of the initial effects shown during the first few days post-partum.

The investigators state, "In all test groups, but particularly among F-1 animals derived from parents treated at 32 or 256mpk, inc'd activity was demonstrated by a pattern including increased mobility and inquisitivity on the hole-board test, a shorter time of tail withdrawal and, reduced maximum performance time on the accelerating rotarod in the absence of bizarre observations or evidence of incoordination in the Irwin screen. The pattern was more clearly evident among males than among females and difference from control values frequently attained statistical significance."

MUTAGENICITY

1. Ames Test

   a) By HRC Labs: BTX at doses up to 1000 ug/plate was tested. Negative results were reported; level of 10,000 ug/plate was toxic to cells.

   b) By Litton Bionetic Labs: At dose levels up to 2000 ug/plate, results were negative in both the non-activated & activated (by S-9 fraction) test systems. Test had been repeated with tester strains TA-1538 & 98, because of initially observed inc'd revertants due to solvent controls.

2. Mouse Lymphoma Forward Mutation Assay: The test material did not induce an inc. in mutations at the TK locus in L5178Y mouse lymphoma cells. Highly toxic treatments at conc'ns up to 500 ug/ml (non-activated) & 1500 ug/ml (S-9 activated) were assayed.

3. Sister Chromatid Exchange (SCE) & Chromosome Aberration Assays in Chinese Hamster Ovary (CHO) Cells: (Litton Bionetics) The test compound was evaluated in terms of ability to induce SCE's & chromosomal aberrations in CHO cells in vitro. Test compound failed to induce sig. inc. in SCE frequency in non-activated; with activation, this frequency was sig. elevated (P less than 0.01) at the highest dose of 1000 ug/ml (considered biologically insig. by the investigator). Test compound was negative in chromosomal aberration assay when tested up to 1000 ug/ml conc'n.

4. In Vitro Transformation of BALB/3T3 Cells Assay: (Litton Bionetics) The test material did not induce any transformed foci over the applied conc'n range of 1-20 ug/ml. This conc'n range corresponded to approx. 80-50% survival in this cytotoxicity test.

5. Micronucleus Test in the Mouse: (HRL Rpt. # BGX/81759, conducted in 1981)

BTX at total dosages of 150, 300 & 500mpk was administered to groups of mice by oral gavage, in 2 equal doses, separated by a 24-hr interval [preliminary study showed maximally tolerated dose (MTD) of 500mpk]. The incidence of micronucleated polychromated erythrocytes at all dosages and at both times of sacrifice was not sig. different from concurrent controls. Mitomycin C was used as a positive control.

OCULAR PHARMACOLOGY

1. Pupillary Activity in the Rabbit: Instilled one drop (0.03 ml) 0.125, 0.25, 0.5 or 1% BTX HCl sol'n; pupil diameter measured up to 3 hrs. There was no effect on pupil diameter.

2. Corneal Sensibility in the Rabbit: Two studies were conducted.

   a) One drop (0.03ml) of 0.125, 0.25, 0.5 & 1% BTX HCl sol'n, equiv. to 37.5, 75, 150 & 300 ug drug, respectively

   b) Two consecutive drops (0.05 ml each) of 0.1, 0.75 & 2% BTX HCl sol'n, equiv. to 100, 750 & 2000 ug drug, respectively.

   Corneal sensibility loss was seen at doses ranging from 100-2000 ug drug; threshold dose for producing loss of corneal sensibility was estimated to be about 100 ug per cornea. Thus, BTX HCl has the ability to cause a partial or full loss of corneal sensibility which is dose-related in intensity, incidence & duration.

3. Intraocular Pressure (IOP) in Rabbits

   a) 0.1-2% BTX HCl sol'n instilled in the eyes of smaller, young normal albino rabbits (1.7-2.3 kg body wt) signficantly lowered IOP at 1 & 2 hrs after 2%, and at 1 hr after 0.75% sol'n; no effect on IOP with 0.1%.

   b) In NZ rabbits, ocular hypertension was induced by intra-ocularly injecting alpha chymotrypsin; 2.0% BTX HCl was then instilled. The response was variable; BTX did cause reduction of IOP in some individual animals.

   c) 0.5% BTX was instilled in the eyes of large normal albino rabbits. There was a definite reduction in IOP, which was stat. sig. at 5 hrs following treatment.

GENERAL PHARMACOLOGY

- BTX may be considered to be a cardioselective beta-blocker; it has a greater affinity for cardiac beta-1 adrenoceptors than for vascular or bronchial beta-2 adrenoceptors. Beta-1 activity was several times greater than beta-2 activity.

- In in vivo studies, doses of BTX producing a blockade of isoproterenol-induced tachycardia did not significantly modify the isoproterenol-induced hypotension - a response known to be mediated by peripheral vascular

beta-2 adrenoceptors. This non-effect would be advantageous clinically, since at least theoretically, respiratory function would be maintained.

- BTX produced an antihypertensive action in spontaneously hypertensive rats and in dogs with renal hypertension. The mechanism, though not fully known, is thought to involve a central and/or peripheral site on the autonomic nervous system.

- BTX administered at doses ensuring beta-adrenoceptor blockade or causing an antihypertensive effect has no obvious undesirable side effects on the CNS, CVS or GI system. Also, BTX does not appear to interfere with drugs clinically used as hypoglycemics (glibenciamide) or anti-coagulants (dicoumarol).

- BTX has no intrinsic sympathomimetic activity.

- BTX has a weak membrane stabilizing action (local anesthetic) - vide supra.

ADME

After oral administration of BTX to M rats (1mpk), dogs (1mpk) & man (20mg total dose), the proportion of unchanged BTX and its metabolites in the urine were:

Compound	% Compound in Urine			Potency Ratio of Metabolites	
	Dog	Rat	Man	Rat	G. Pig
BTX	3.2	1.0	15.5	1.0	1.0
SL 77.009	-	-	*	< 5	-
SL 77.010	28.2	61.6	23.9	0.003	< 0.02
SL 77.310	2.5	2.7	3.0	0.04	0.068
SL 80.0088	6.8	4.9	trace	0.03	0.04
SL 80.0827	4.1	12.1	-	0.001	0.004

*Measurable

Metabolites of BTX had very little beta-adrenoceptor blocking activity.

SUMMARY: The following animal toxicity studies were reviewed:

TOPICAL OCULAR TOXICITY

Ocular safety was studied following instillation of the ophthalmic solution ranging from 1 month to 1 year in the rabbit. In the 1-month study in rabbits, with concentration up to 2.5% BTX, no ocular irritation was observed; no lesions related to drug treatment were reported. In the 1-year topical ocular study in rabbits with 0.5% BTX ophthalmic solution (2 drops, 2x/day), eyes were examined by slit lamp at 2-week intervals as well as by indirect ophthalmoscopy. Minimal to moderate conjunctival irritation was reported. Histologically, donut-shaped vacuoles along the suture line of the lens were reportedly not cataracts. The significance of these vacuoles is not known, according to the investigators.

SYSTEMIC TOXICITY

Acute Toxicity

	Route	Species	Sex	LD_{50} (mpk)	Clinical Signs
BTX	Oral	Mouse	M	350 ± 23	tremors, convulsions,
			F	400 ± 30	stereotype behavior,
	"	Rat	M	980 ± 95	motor difficulties
			F	860 ± 113	
	IV	Mouse	M	40 ± 1.15	
			F	55 ± 2.0	
	"	Rat	M	28 ± 1.6	
			F	25 ± 1.5	
BTX Ophth Sol'n	IV	Mouse		42.6 (free base)	
	Oral	Mouse		482.7mpk (admin. as 2.5% sol'n)	

SUBACUTE TOXICITY

BTX was administered orally (gavage) to rats at doses of 50, 100 & 200mpk in males and 25, 50 & 100mpk in females, for 4 weeks. The "no effect" dose was 25mpk. BTX produced a dose-related increase in serum urea & creatinine levels. Histopathologically, no abnormality was reported at 100mpk in males or at 200mpk in females.

Doses of 2, 6 & 15mpk IV to rats for 4 weeks caused no mortality. Clinical symptoms at 15mpk within 5 minutes following injection were agitation, unsteady gait, irregular breathing, and piloerection & tremors in a few animals. At 15mpk, there was also reduced body weight associated with reduced food intake. Ophthalmoscopy, blood chemistry, urinalysis and histopathology were within normal range.

BTX was administered IV to dogs for 4 weeks, at 1, 2 & 6mpk (2 dogs injected with 10mpk died; cause of death could not be established). Clinical signs observed were ataxia & salivation at 6mpk. Also at 6mpk, significantly reduced heart rates were noted after 3 weeks. Body weight, food intake, ophthalmoscopy, urinalysis and pathology were negative.

CHRONIC TOXICITY

Rats were treated by oral gavage at dose levels of 1.5, 2.5, 25 & 400mpk/day for 26 weeks. At 1.5 & 2.5mpk, there was intermittent salivation after dosing, lasting for 20 minutes. The HD (400mpk) produced the following results: (a) About half of the animals died (excluding 10/sex killed at interim sacrifice), some with foci of alveolar macrophages; in others the cause of death could not be established. (b) Body weight gain was slightly reduced. (c) Ophthalmological and hematological exams were normal. (d) Moderate increases were noted in alkaline phosphatase, kalemia and urine volume. (e) Adrenal, liver, kidney, spleen & uterus weights were significantly increased. (f) Histologically, treatment-related lesions were: epithelial hyperplasia in the urinary bladder (noted first in 13-week interim sacrifice); follicular hyperplasia of the thyroid; absence of vacuolation of centrilobular hepatocytes in males; diffuse chronic inflammatory cell

infiltration of the myocardium, degeneration of occasional mycardial fibers and deposition of cartilage in chordae tendinae (indirect pharmacologic effect); engorgement of red pulp in the spleen with blood (a change in hemodynamic status of the spleen); in the kidneys a possible effect was localization of minor tubular changes and associated chronic inflammatory cell infiltration in the juxta-medullary region of the renal cortex considered to represent the early stages of development of a specific lesion in this locality (no further explanation).

Rats were treated by oral gavage for 61 weeks at doses of 6, 25 & 100mpk/day. The study was originally planned for 78 weeks, but because of inflammatory lesions of the posterior legs of all animals (treated & controls) which appeared in the 28th wk of dosing, the investigator decided to terminate the study early at 61 weeks. Moderate decrease in body weight gain was reported in HD & MD males. Hematology, blood chemistry, urinalysis and histopathology were within normal limits or considered not related to treatment.

A 26-week study was performed in dogs at doses of 2, 6 & 20mpk/day via oral capsules. There was no mortality. One HD dog showed convulsions on isolated occasions and others showed head nodding movements, vomiting and salivation. All treated groups showed significant reductions in heart rate. Ophthalmological exam (Schirmer Tear Test) showed a significant decrease in lacrimal secretion. This decrease, attributed to excessive pharmacological action of beta-blockers, induced a certain number of minor epithelial erosions of the cornea. Histologically, adipose tissue replaced glandular acini of the lacrimal gland in 2 LD & 2 MD dogs. Hematology and urinalysis were normal. Serum urea level was increased at the HD.

A 52-week oral study in dogs at 2, 6 & 20mpk/day produced the following results: One HD dog died on day 4 of dosing; there was no obvious cause of death. Symptomology was the same as in the 26-week study. Ophthalmoscopic exam and Schirmer Tear Test showed a decrease in lacrimal secretion at the HD. Histologically, no abnormality was found in the lacrimal glands. Heart rate decreased in the HD dogs in the second half of the study. Blood pressure (systolic) was slightly decreased in MD & HD dogs. BUN was elevated at the HD in the later stages of the study. Hematology, urinalysis, gross & histopathology were reported to be within normal limits.

CARCINOGENICITY

In a 2-year oral (dietary admix) study, groups of CD Sprague-Dawley rats (50/sex/group) were fed BTX at 3, 12 or 48mpk/day; 2 control groups received untreated diet. The rats were dosed for 104 weeks. The HD group showed reduced body weight gains and marginally reduced food intake. Statistically. significant changes at 95% confidence level were:

a) Males: dose-related mortality, particularly at the HD; dose-related reduced incidence of pituitary tumors in treated animals, particularly marked at the HD;

b) Females: increased incidence of skin tumors at the LD only; increased incidence of adrenal medullary tumors at the MD only; increased incidence of liver tumors at the MD only;

c) Sexes combined: dose-related reduced mortality in treated rats, but markedly so at the HD; reduced pituitary tumor incidence in treated animals, most marked at the HD, but also significant at the LD; increased incidence of malignant skin tumors at the MD.

In a 2-year (102 week) oral (dietary admix) study, groups of CD-1 Swiss mice (50/sex/group) were fed BTX at dose levels of 6, 20 & 60mpk/day. Mice were dosed for 102 weeks. The following effects, significant at the 95% confidence level, were seen:

a) Males: reduced mortality at the LD only;

b) Females: reduced incidence of definitely malignant lung tumors at the LD only; reduced incidence of malignant tumors of any site at the LD only;

c) Sexes combined: reduced mortality at the LD only; reduced incidence of tumors of other sites (testes, spleen, pancreas, etc.) at the MD only; reduced incidence of malignant tumors of any site at the LD only. The only site where there was increased incidence at the HD was the uterus, with both vascular and non-vascular tumors, but the level of significance was weak (90% confidence level) and that, too, only in some statistical comparisons.

REPRODUCTION

In a Segment I fertility study, BTX was tested orally (gavage) in rats at levels of 4, 32 & 256mpk/day. The males were dosed from 9 weeks preceding and during mating. The females were dosed from 2 weeks preceding mating, through mating, and up to day 20 of gestation. There was no effect on reproductive capability in females or on male fertility. In the HD females, clinical toxic signs, 16% mortality and a highly significant increase in embryonic/fetal death was noted. In the MD females, there was no embryonic/fetal mortality, but fetal, litter, and pup weights were lowered, and there were marginal delays in startle response and vaginal opening, which may or may not be relevant. The LD produced slightly lower mean fetal weight and lower litter weight. These effects occurred after implantation and were seen in dams killed on day 20 of gestation.

A Segment II teratology study was performed in rats, in which BTX was administered orally (gavage) at doses of 4, 40 & 400mpk/day, days 6-15 of gestation. At the LD & MD, though clinical signs (salivation) were seen post-dosing, there was no effect on the conceptus. At the HD, the incidence of embryonic death was significantly increased, and correlating with a reduction in fetal weight was a high incidence of fetuses showing varying degrees of visceral and skeletal changes, apparently a consequence of fetal retardation. Even occasional frank malformations (cleft palates in 3 fetuses) were considered to be due to this retardation.

A Segment II oral (gavage) study was performed in rats by Synthelabo. Two separate experiments were done: (a) BTX dosed at 200 & 400mpk (7/13 died at 400mpk and treatment was stopped on day 13); (b) BTX at 10 & 200mpk. Effects on reproduction were as follows: no effect at 10mpk; at 200mpk, slightly increased post-implantation loss; no malformations, delayed ossification &

extra ribs at an incidence comparable to controls; at 400mpk, total fetal resorption.

In a Huntingdon study, rabbits were dosed orally (gavage) at 4, 12 & 36mpk/day, on days 6-18 of pregnancy. About 30% of the animals in each treated group died (enteric disorder); 5% controls died. Among the survivors, the incidence of total litter loss (resorption/abortions) was 0, 14, 8 & 57% in controls, LD, MD & HD groups, respectively. Alternatively, deaths & exclusions (except those due to non-enteric causes), total litter losses may be combined to provide incidence of pregnancy failures. Such incidences were 7, 37, 42 & 67% in controls, LD, MD & HD, respectively, indicating that, though the effects were greatest at the HD, the may also have been induced at the LD & MD. No major anomalies were reported.

Life Science Research U.K. conducted a study in rabbits in which BTX was administered orally (gavage) at 1, 4, 12 & 36mpk. Two abortions/total litter loss at 36mpk and one abortion at 12mpk occurred. Post-implantation losses (primarily late resorption) were 54.4 (statistically significant), 10.6, 3.0 & 3.4% in rabbits dosed at 36, 12, 4 & 1mpk, respectively, compared with 15.4% in controls. No malformations were reported.

A peri- & post-natal study was performed in rats in which BTX was administered at 4, 32 & 256mpk orally (gavage) from day 15 of gestation to day 21 post-partum. At 4 & 32mpk there were drug effects on the mother, but not on the fetus. At 256mpk, maternal toxicity and high incidence (79%) of total litter loss occurred either perinatally or immediately post-natally. Among the surviving pups, lower body weight gain and slightly delayed development were noted.

MUTAGENICITY

A battery of *in vitro* tests were conducted. BTX at the highest dose tested, 1000 ug/ml (and with activation), produced a statistically significant increase in sister chromatid exchanges in Chinese Hamster Ovary cell assay. Effects were not statistically significant in the non-activated system at this, or lower doses. Results were negative for chromosomal aberrations in this assay. Other *in vitro* tests with negative results were the Ames test and mouse lymphoma forward mutation assay. No effects were reported in the *in vivo* micronucleus test in mice conducted at doses up to 500mpk (maximum tolerated dose).

COMMENTS & RECOMMENDATION

1. Betaxolol (BTX), a beta adrenergic blocking agent, was originally developed by Synthelabo (Laboratoires d'Etudes et de Recherche; LERS), Paris, France. The basic pharmacological, toxicological & clinical investigations for systemic use were conducted by them.

2. The applicant proposes to use a racemic mixture of 50:50 of (S)- and (R)-isomers of BTX. Pharmacologically, the (S) isomer is more active.

3. The vehicle ingredients are commonly used compounds and are not likely to pos safety hazards.

4. One drop (0.06ml) of the 0.5% solution contains 0.33mg of BTX. Thus, daily human exposure of one drop in each eye twice daily would be 1.32mg (0.33 x 2 x 2 = 1.32). Even assuming 100% absorption, the systemic exposure on a mg/kg basis would be quite small.

   In 4-week IV toxicity studies, 6mpk in the rat & 3mpk in the dog were the "no toxic effect" dose levels (IV route closely simulates absorption from topical ophthalmic solutions). Thus, on a subacute basis, BTX was fairly well-tolerated. In chronic (26 week) rat studies at 1.5 & 2.5mpk orally, salivation was observed, but no lesions were reported; target organ toxicity was observed at 400mpk (about one-half died at this dose).

   The applicant should incorporate in the labelling: (a) an accurate statement regarding the embryotoxicity/fetotoxicity (a post-implantation effect) noted in the segment II rat & rabbit teratology studies, and (b) an indication that the carcinogenicity studies may not have employed the highest tolerated dose.

   I have no objection from a safety standpoint to the approval of this application, provided the recommended labelling changes are made.

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

cc: Orig. NDA
HFN-815
HFN-815/MO
CSO
HFN-340
HFN-815/SRJoshi/smc/5/3/85
R/d init.by:JMDavitt
3488b

APPENDIX I

Incidence of Males with Benign & Malignant Tumors (Mice)

Benign - Males

mg SL 75 212-10/kg/day	0	0	6	20	60
Number of Animals Examined	46	49	48	50	49
Liver	3 (7)	4 (8)	5(10)	7(14)	5(10)
√Lungs	10(22)	10(20)	14(29)	11(22)	12(24)
√Thyroids	1 (3)	1(2)	0	0	0
√Adrenals	2 (5)	0	2 (5)	3 (7)	1 (2)
√Pituitary	0	0	0	0	1 (3)
Harderian gland **	0	0	1 (2)	0	0
Tested	1 (2)	0	1 (2)	0	
Bone and joints	0	2 (4)	3 (6)	0	1 (3)
Skin **	0	1 (2)	1 (2)	0	1 (2)
Number of animals with benign tumours (including indeterminate lung tumours†)	15(33)	14(29)	22(46)	17(34)	18(37)

Benign - Females

mg SL 75 212-10/kg/day	0	0	6	20	60
Number of Animals Examined	43	46	48	50	47
Liver	1 (2)	2 (4)	2 (4)	2 (4)	2 (4)
Lung	6(15)	8(17)	10(21)	8(16)	5(11)
Lymph nodes	0	0	0	0	1 (2)
Salivary glands	0	0	1 (2)	0	0
Stomach	0	1 (2)	0	0	0
Pancreas	0	0	1 (2)	0	1 (2)
Adrenals	0	2 (5)	0	0	0
Pituitary	1 (3)	2 (5)	2 (5)	2 (4)	3 (7)
Harderian gland **	1 (3)	0	0	0	0
Ovaries	1 (2)	4 (9)	3 (7)	6(12)	1 (2)
Uterus	2 (5)	1 (2)	2 (4)	0	3 (7)
Mammary gland	0	0	1 (3)	0	4(10)
Bone	0	1 (2)	1 (2)	0	1 (2)
Abdominal fat	1 (2)	1 (2)	0	0	0
Number of animals with benign tumours (including indeterminate lung tumours†)	11(26)	18(39)	17(35)	16(32)	15(32)

Malignant - Males

mg SL 75 212-10/kg/day	0	0	6	20	60
Number of Animals Examined	46	49	48	50	49
Liver	11(24)	12(24)	15(31)	12(24)	8(16)
Lung	5(11)	2 (4)	5(10)	5(10)	6(12)
Spleen	0	0	0	0	1 (2)
Lymph nodes **	0	1 (2)	0	0	0
Lymphoma **	4 (9)	4 (8)	2 (4)	4 (8)	6(12)
Disseminated sarcoma **	0	0	0	0	1 (2)
√Thyroids	0	2 (4)	0	0	0
√Adrenals	0	1 (2)	0	1 (2)	1 (2)
Brain	0	1 (2)	0	0	0
Bone	0	0	0	2 (4)	0
Peritoneum**	0	1 (2)	0	0	0
Skin **	0	4 (8)	1 (2)	3 (6)	4 (8)
Number of animals with malignant tumours	19(41)	25(51)	21(44)	22(44)	22(45)

Malignant - Females

mg SL 75 212-10/kg/day	0	0	6	20	60
Number of Animals Examined	43	46	48	50	47
Liver	1 (2)	1 (2)	3 (6)	3 (6)	2 (4)
Lungs	6(15)	4 (9)	0	3 (6)	2 (4)
Spleen	0	1 (2)	0	0	0
Thymus	0	1 (2)	0	0	0
Lymphoma **	8(19)	11(24)	6(13)	6(12)	10(21)
Multiple organ **	2 (5)	0	3 (6)	1 (2)	0
Stomach	0	0	1 (2)	0	0
Ovaries	1 (2)	0	0	0	0
Uterus	1 (2)	0	1 (2)	0	4 (9)
Mammary gland	4(14)	7(17)	4(10)	8(19)	5(12)
Abdominal fat **	0	0	0	0	1 (2)
Skin **	1 (2)	2 (4)	0	1 (2)	1 (2)
Number of animals with malignant tumours	21(49)	27(59)	17(35)	21(42)	24(51)

APPENDIX II

Histopathological Lesions in Male Swiss Mice in 2-Year Dietary Admix Carcinogenicity Study of SL 75 212-10

	All Animals				
mg SL 75 212-10/kg/day	0	8	6	20	60
Number of Tissues Examined	46	49	48	49	49
LIVER					
HEPATOCELLULAR CARCINOMA	10(24)	12(24)	15(31)	12(24)	8(16)
HEPATOCELLULAR ADENOMA	3 (7)	4 (8)	5(10)	7(14)	5(10)
METASTASIS FIBROSARCOMA	0	1 (2)	0	0	0
METASTASIS ANGIOSARCOMA	0	1 (2)	0	0	2 (4)
Non-neoplastic area/focus	4 (9)	0	4 (8)	1 (2)	1 (2)
Hypertrophy hepatocellular	1 (2)	0	4 (8)	2 (4)	0
Hyperplasia hepatocellular	2 (4)	0	0	1 (2)	0
Cytoplasmic vacuolation/ degeneration, hepatocellular	9(20)	4 (8)	7(15)	3 (6)	2 (4)
Necrosis/infarction	6(13)	0	0	6(12)	0
Bile ductule hyperplasia	1 (2)	0	0	0	0
Hepatitis	9(20)	19(31)	13(27)	11(22)	10(20)
Angiectasis	2 (4)	0	0	0	1 (2)
Lymphoid hyperplasia	0	1 (2)	0	0	0
Haemopoiesis	0	2 (4)	0	2 (4)	2 (4)
Haemorrhagic cyst	1 (2)	1 (2)	0	0	0
Number of Tissues Examined	46	49	48	49	49
KIDNEYS					
METASTASIS FIBROSARCOMA	0	1 (2)	0	0	0
METASTASIS ADENOCARCINOMA (NOS)	0	0	1 (2)	0	0
METASTASIS ADRENAL TUMOUR	0	0	0	0	1
Chronic nephropathy	30(65)	27(55)	29(60)	29(59)	30(61)
Nephritis	1 (2)	2 (4)	1 (2)	1 (2)	0
Hydronephrosis	4 (9)	2 (4)	0	2 (4)	2 (4)
Vasculitis	0	2 (4)	0	0	0
Amyloid	1 (2)	0	2 (4)	2 (4)	1 (2)
Lymphoid hyperplasia	0	1 (2)	1 (2)	0	0

	All Animals				
mg SL 75 212-10/kg/day	0	[illegible]	6 [illegible]	20	60
Number of Tissues Examined	45	49	48	50	49
LUNGS AND BRONCHI					
ALVEOLOGENIC TUMOUR (M)	5(11)	2 (4)	4 (8)	4 (8)	6(12)
ALVEOLOGENIC TUMOUR MALIGNANCY INDETERMINATE †	10(22)	10(20)	14(29)	11(22)	12(24)
METASTASIS HEPATOCELLULAR CARCINOMA	0	4 (8)	0	0	0
METASTASIS FIBROSARCOMA	0	1 (2)	0	1 (2)	0
ADENOCARCINOMA (NOS)	0	0	1 (2)	1 (2)	0
Lymphoid hyperplasia	0	1 (2)	3 (6)	1 (2)	0
Adenomatosis	0	0	1 (2)	0	0
Interstitial pneumonitis	9(20)	8(16)	4 (8)	4 (8)	12(24)
Vascular congestion	4 (9)	5(10)	3 (6)	3 (6)	3 (6)
Alveolar macrophage hyperplasia	6(13)	3 (6)	2 (4)	1 (2)	3 (6)
Pneumonia	0	0	2 (4)	2 (4)	4 (8)
Pleurisy	0	3 (6)	1 (2)	1 (2)	0
Vasculitis	0	1 (2)	0	0	0
Alveolar haemorrhage	1 [illegible]	0	0	0	0
Necrosis	0	[illegible] (2)	0	0	0
Number of Tissues Examined	44	50	48	50	49
CARDIOMYOPATHY	13(30)	8(16)	14(29)	8(16)	10(20)
Number of Tissues Examined	39	44	44	45	47
ADRENALS					
CORTICAL CARCINOMA	0	1 (2)	0	1 (2)	0
CORTICAL ADENOMA	2 (5)	0	2 (5)	1 (2)	1 (2)
MALIGNANT ADRENAL TUMOUR	0	0	0	0	1 (2)
BENIGN PHAEOCHROMOCYTOMA	0	0	0	2 (4)	0
Hyperplasia, subcapsular cells	1(29)	10(23)	7(17)	4 (9)	14(30)
Hyperplasia, medullary cells	0	0	1 (2)	0	3 (6)
Cortical foci	2 (5)	3 (5)	2 (5)	3 (7)	4 (9)

Pathological Lesions in Female Swiss Mice in 1 Year Dietary Admix Carcinogenicity Study of SL 75 212-10

APPENDIX II

	All Animals				
mg SL 75.212-10/kg/day	0	0	6	20	60
Number of Tissues Examined	41	45	48	50	47
LUNGS AND BRONCHI					
ALVEOLOGENIC TUMOUR (M)	6(15)	3 (7)	0	3 (6)	2 (4)
ALVEOLOGENIC TUMOUR MALIGNANCY INDETERMINATE	6(15)	8(18)	10(21)	8(16)	5(11)
MALIGNANT NEOPLASM (NOS)	0	1 (2)	0	0	0
METASTASIS SARCOMA (SINUSITIS)	0	0	0	1 (2)	0
METASTASIS ENDOMETRIAL ADENOCARCINOMA	1 (2)	0	0	0	0
METASTASIS MAMMARY ADENOCARCINOMA	0	3 (7)	2 (4)	0	1 (2)
METASTASIS MAMMARY ADENOCANTHOMA (M)	0	0	1 (2)	3 (6)	0
METASTASIS TO RIB CAGE OF ALVEOLOGENIC TUMOUR (M)	1 (2)	0	0	0	0
Adenomatosis	0	0	0	0	(2)
Interstitial pneumonitis	7(17)	5(11)	3 (6)	7(14)	5(11)
Bronchitis	1 (2)	0	0	0	0
Vascular congestion	4(10)	4 (9)	3 (6)	7(14)	6(13)
Alveolar macrophage hyperplasia	7(17)	4 (9)	3 (6)	6(12)	3 (6)
Pneumonia	0	0	1 (2)	0	1 (2)
Pleurisy	2 (5)	2 (4)	1 (2)	1 (2)	0
Vasculitis	0	0	0	1 (2)	0
Alveolar haemorrhage	0	0	0	1 (2)	0
Thrombosis	0	0	0	0	1 (2)
Lymphoid hyperplasia	1 (2)	1 (2)	0	1 (2)	0
Number of Tissues Examined	41	43	41	48	45
ADRENALS					
CORTICAL ADENOMA	0	2 (5)	0	0	0
Hyperplasia, subcapsular cells	25(61)	16(37)	13(32)	27(56)	27(60)
Cortical foci	0	0	0	1 (2)	0
Cystic	0	1 (2)	0	0	0
Amyloidosis change	0	0	1 (2)	0	0
Number of Tissues Examined	38	41	40	47	42
PITUITARY					
ADENOMA	1 (3)	2 (5)	2 (5)	2 (4)	3 (7)
Hyperplasia, adenohypophysis	0	0	0	0	1 (2)
Hypertrophy	0	0	0	0	1 (2)

Histopathological Lesions in Female Swiss Mice in 2-Year Dietary Admix Carcinogenicity Study of SL 75 212-10

APPENDIX IV

mg SL 75 212-10/kg/day	0	0	6	20	60
Number of Tissues Examined	42	44	48	50	47
LIVER					
HEPATOCELLULAR CARCINOMA	1 (2)	0	3 (6)	3 (6)	2 (4)
HEPATOCELLULAR ADENOMA	1 (2)	2 (5)	2 (4)	2 (4)	2 (4)
ANGIOSARCOMA	0	1 (2)	0	0	0
Non-neoplastic area/focus	0	2 (5)	1 (2)	1 (2)	0
Cytoplasmic vacuolation/ degeneration hepatocellular	5(12)	9(20)	6(12)	5(10)	2 (4)
Necrosis/infarction	3 (7)	3 (7)	3 (6)	0	1 (2)
Hepatitis	6(14)	7(16)	8(17)	12(24)	11(23)
Angiectasis	1 (2)	0	4 (8)	0	0
Lymphoid hyperplasia	0	0	0	0	1 (2)
Haemopoiesis	2 (5)	1 (2)	2 (4)	2 (4)	2 (4)
Number of Tissues Examined	43	45	48	50	47
KIDNEYS					
Chronic nephropathy	31(72)	24(53)	30(63)	34(68)	31(66)
Nephritis	4(15)	2 (4)	0	1 (2)	2 (4)
Hydronephrosis	0	2 (4)	0	1 (2)	2 (4)
Focal necrosis/infarction	0	0	1 (2)	0	1 (2)
Vasculitis	0	0	0	0	1 (2)
Amyloid	2 (5)	0	0	1 (2)	3 (6)
Lymphoid hyperplasia	0	0	0	0	1 (2)
Cyst	0	0	1 (2)	0	0
Number of Tissues Examined	43	46	48	50	47
HEART AND MAJOR VESSELS					
METASTASIS SARCOMA	0	0	0	1 (2)	0
METASTASIS MAMMARY ADENOCARCINOMA	0	0	0	1 (2)	0
METASTASIS LUNG TUMOUR (M)	0	0	0	0	1 (2)
Cardiomyopathy	10(23)	5(11)	11(23)	7(14)	1 (2)
Inflammation epicardium/ pericardium	2 (5)	0	2 (4)	0	0
Inflammation endocardium	0	1 (2)	0	2 (4)	0
Inflammation myocardium	0	1 (2)	0	0	0
Atrial thrombus	1 (2)	1 (2)	1 (2)	0	0
Vasculitis/perivasculitis	3 (7)	1 (2)	3 (6)	0	0
Vascular thrombus	1 (2)	0	1 (2)	0	0
Calcification vessel walls	0	0	0	0	1 (2)
Haemorrhage	0	0	2 (4)	0	0

APPENDIX V

Histopathological Lesions in Female Swiss Mice in 2-Year Dietary Admix Carcinogenicity Study of SL 75 212-10

	All Animals				
mg SL 75-212-10/kg/day	0	0	6	20	60
Number of Tissues Examined	41	44	45	49	46
OVARIES					
TUBULAR ADENOMA	0	0	0	1 (2)	0
GRANULOSA CELL TUMOUR (M)	1 (2)	0	0	0	0
GRANULOSA CELL TUMOUR (B)	0	0	0	1 (2)	0
MIXED THECA-GRANULOSA CELL TUMOUR	1 (2)	1 (2)	0	0	0
CYSTADENOMA	0	3 (7)	3 (7)	4 (8)	1 (2)
Cystic	34(83)	24(55)	24(53)	22(45)	22(48)
Atrophy	0	0	0	0	1 (2)
Luteal hyperplasia	0	1 (2)	1 (2)	0	1 (2)
Angiomatous change	2 (5)	1 (2)	2 (4)	2 (4)	1 (2)
Inflammatory change	0	2 (5)	0	2 (4)	0
Haemorrhage in ovarian ligament	0	1 (2)	0	1 (2)	0
Number of Tissues Examined	29	39	39	42	41
MAMMARY GLAND					
ADENOCARCINOMA	4(14)	6(14)	3 (8)	8(19)	5(12)
ADENOACANTHOMA (M)	0	0	1 (3)	0	0
ADENOACANTHOMA (B)	0	0	0	0	3 (7)
CARCINOSARCOMA	0	1 (2)	0	0	0
FIBROADENOMA	0	0	1 (3)	0	0
ADENOMA	0	0	0	0	1 (2)
Hyperplasia/secretion	4(14)	4(10)	6(15)	5(12)	6(14)
Duct ectasia	1 (3)	0	0	0	0
Mastitis	2 (7)	1 (2)	2 (5)	0	2 (5)
Number of Tissues Examined	41	43	45	47	46
UTERUS					
ADENOCARCINOMA	1 (2)	0	0	0	1 (2)
STROMAL SARCOMA	0	0	0	0	1 (2)
LEIOMYOMA	0	0	1 (2)	0	1 (2)
ANGIOSARCOMA	0	0	1 (2)	0	2 (4)
ANGIOMA	1 (2)	0	0	0	0
UTERINE POLYP	0	1 (2)	1 (2)	0	2 (4)
CYSTADENOMA	1 (2)	0	0	0	0
Cystic endometrial hyperplasia	20(49)	24(56)	24(53)	20(42)	27(59)
Suppurative metritis	1 (2)	1 (2)	0	0	1 (2)
Angiomatous stroma	0	1 (2)	2 (4)	1 (2)	0
Polypoid growths	0	0	1 (2)	0	1 (2)
Hydrometra	1 (2)	0	0	0	0

APPENDIX VI

Incidence in Rats with Benign & Malignant Tumors
2-Year Oral(dietary admix) Study with SL 75212

Males-Benign					
mg SL 75 212-10/kg/day	0	0	3	12	48
Number of animals Examined	50	50	50	50	50
Thyroids (follicular cells)	3 (6)	2 (4)	-	-	2 (4)
Thymus	1 (2)	-	-	-	-
Pancreas (endocrine)	3 (6)	3 (6)	3 (6)	3 (6)	3 (6)
Pancreas (exocrine)	2 (4)	-	2 (4)	1 (2)	-
Adrenals	2 (4)	4 (8)	3 (6)	4 (8)	3 (6)
Pituitary	24 (49)	26(52)	24(48)	19 (40)	18 (37)
Mammary gland	-	1 (2)	-	-	1 (2)
Testes	1 (2)	1 (2)	2 (4)	-	4 (8)
Skin **	2 (4)	4 (8)	1 (2)	7(14)	2 (4)
Lymph nodes **	-	-	-	-	1 (2)
Number of animals with benign tumours	28(56)	30(60)	27(54)	26(52)	29(58)

Females-Benign					
mg SL 75 212-10/kg/day	0	0	3	12	48
Number of animals Examined	50	50	50	50	50
Thymus	-	-	1 (2)	-	-
Thyroids (follicular cells)	-	3 (6)	-	1 (2)	-
Parathyroids	2 (4)	-	-	-	1 (2)
Intestines	1 (2)	-	-	1 (2)	-
Pancreas (endocrine)	2 (4)	1 (2)	1 (2)	1 (2)	1 (2)
Pancreas (exocrine)	2 (4)	-	1 (2)	1 (2)	-
Adrenals	4 (8)	-	1 (2)	1 (2)	1 (2)
Ovary	1 (2)	-	-	-	1 (2)
Uterus	2 (4)	2 (4)	1 (2)	1 (2)	1 (2)
Pituitary	23(47)	23(46)	16(33)	23(48)	29(58)
Mammary glands	11(24)	12(24)	17(35)	16(33)	10(20)
Skin**	2 (4)	-	3 (6)	-	2 (4)
Brain	-	-	-	-	1 (2)
Bladder	1 (2)	-	-	-	-
Number of animals with benign tumours	36(72)	31(62)	30(60)	36(72)	37(74)

Males-Malignant					
mg SL 75 212-10/kg/day	0	0	3	12	48
Number of animals Examined	50	50	50	50	50
Liver	3 (6)	1 (2)	4 (8)	-	3 (6)
Kidneys	-	-	1 (2)	-	-
Heart	-	-	1 (2)	1 (2)	-
Lung	1 (2)	-	1 (2)	-	-
Salivary gland	-	1 (2)	-	-	-
Thyroids (C cell)	4 (8)	1 (2)	2 (4)	5(10)	1 (2)
Stomach	1 (2)	-	-	-	-
Intestines	-	-	-	1 (2)	-
Pancreas (endocrine)	-	-	1 (2)	1 (2)	-
Adrenal cortex	-	1 (2)	1 (2)	-	2 (4)
Adrenal medulla	10(20)	20(40)	12(24)	15(30)	19(38)
Testes	-	-	-	2 (4)	-
Pituitary	3 (6)	5(10)	3 (6)	4 (8)	4 (8)
Mammary glands	2 (4)	-	-	-	1 (2)
Skin **	-	3 (6)	4 (8)	4 (8)	4 (8)
Brain	3 (6)	2 (4)	2 (4)	2 (4)	1 (2)
Lymph nodes **	-	1 (2)	-	-	1 (2)
Lymphoma **	-	1 (2)	1 (2)	-	2 (4)
Number of animals with malignant tumours	18(36)	30(60)	27(54)	28(56)	28(56)

Females-Malignant					
mg SL 75 212-10/kg/day	0	0	3	12	48
Number of Animals Examined	50	50	50	50	50
Liver	-	-	1 (2)	4 (8)	2 (4)
Kidneys	-	-	-	1 (2)	-
Lung	1 (2)	-	1 (2)	-	-
Thyroids (follicular cells)	-	-	-	1 (2)	-
Thyroids (C cells)	1 (2)	1 (2)	2 (4)	3 (6)	4 (8)
Stomach	-	-	1 (2)	-	-
Intestines	1 (2)	-	-	-	-
Pancreas (endocrine)	-	-	-	-	1 (2)
Adrenal cortex	4 (8)	2 (4)	-	5(10)	2 (4)
Adrenal medulla	5(10)	2 (4)	4 (8)	9(18)	5(10)
Ovary	-	2 (4)	-	-	-
Uterus	-	2 (4)	-	-	3 (6)
Pituitary	17 (35)	16 (33)	15(33)	16(33)	12(24)
Mammary glands	8 (16)	8(16)	6(13)	3 (6)	8(16)
Skin**	-	1 (2)	3 (6)	3 (6)	-
Brain**	2 (4)	1 (2)	1 (2)	3 (6)	1 (2)
Lymphoma **	1 (2)	1 (2)	2 (4)	-	-
Number of animals with malignant tumours	28(56)	28(56)	26(56)	[illegible]	25(50)

STAT

REV

Statistical Review and Evaluation

Date: APR 16 [illegible]

NDA #: 19-270/Drug Class: 1B

Applicant: Alcon Laboratories

Name of Drug: Betaxolol Ophthalmic Solution

Documents Reviewed: Volumes 1.2 - 1.8 dated 4/26/84

The medical reviewer for this NDA is Dr. Harper (HFN-140) with whom this statistical review has been discussed.

I. Background

This NDA was submitted to establish the efficacy and safety of Betaxolol Ophthalmic Solution in the treatment of glaucoma.

Betaxolol, a cardioselective beta adrenergic blocker, has a selective beta-1 adrenergic blocking property which the sponsor believes may lead to increased safety and to better control of intra ocular pressure (IOP) than currently marketed products for the treatment of glaucoma.

Four multicenter studies were conducted to assess the efficacy and safety of Betaxolol in the treatment of patients suffering from glaucoma or ocular hypertension: (a) Protocol 79-E-11 compared Betaxolol (0.25%) to placebo in reducing IOP; (b) Protocol 79-E-23 compared Betaxolol (0.5%) to Timolol (0.5%) in reducing IOP; (c) Protocol C-82-24 compared the effects of a single dose of Betaxolol (1.0%) and Timolol (0.5%) with placebo on blood pressure and pulse rate during a 10-minute treadmill exercise test; (d) Protocol C-81-25 evaluated the effects of a single dose of Betaxolol (1%) and Timolol (0.5%) in comparison with placebo on pulmonary parameters in patients with reactive airway disease who demonstrated a systemic response to ocular Timolol 0.5% as evidenced by a 15% reduction in FEV_1.

II. Study Design and Statistical Methods

The design features of these 4 studies are summarized below:

Table 1: Summary of Study Design

Study Description / Clinical Objective	Controlled Clinical Trials			
	79-E-11	79-E-23	C-82-24	C-81-25
	Reduction of IOP	Reduction of IOP	Effects on BP and pulse	Effects on BP and pulse
Study Design	R, DB, P	R, DB, P	R, DB, Latin Square	R, DB, Crossover
Study Subject	glaucoma or ocular hypertension	glaucoma or ocular hypertension	Normal Volunteers	Reactive Airway Disease
Control Substance	Placebo	Timolol 0.5%	Timolol 0.5% and placebo	Timolol 0.5% and placebo
Dose Regimen	0.25%, BID	0.5% BID	1%, single dose	1% single dose
Washout Period	Until mean IOP $\geq$ 2.5 mmHg	Same as 79-E-11	7 days	3 days
Study Duration	6 weeks	26 weeks	3 weeks	4 weeks
No. of investigators	6	11	2	1
Enrollment*	49/53	132/137	24	9
Efficacy Evaluable* Sample Size	44/47	93/95	24	9
Visit at weeks	1, 2, 4, 6	1, 2, 4, 6, 8, 17, 26	--	--
Primary Efficacy Variables	IOP	IOP	--	--
Primary Safety Variables	Pulse, MAP Pupil Diameter Basal Tear Secretion	Pulse, MAP Pupil Diameter Basal Tear Secretion	Pulse BP	FEV_1, FVC FEF_{25-75} Respiratory rate, MAP, Pulse

Note: Abbreviations: R = Randomized; DB = Double Blind; P = Parallel groups; IOP = Intraocular Pressure; and MAP = Mean Arterial Blood Pressure.

* Number of patients: "Betaxolol"/"Control"

Both Studies 79-E-11 and 79-E-23 were conducted using a randomized, parallel group, double-blind design. Betaxolol was given twice a day in 0.25% solution in Study 79-E-11 and 0.5% solution in Study 79-E-23. The primary efficacy variable for these studies was IOP which was measured at baseline, weeks 1, 2, 4, and 6 in Study 79-E-11 and at baseline, weeks 1, 2, 4, 6, 17, and 26 in Study 79-E-23. Systemic safety data included pulse rate and mean arterial blood pressure (MAP), while pupil diameter and basal tear secretion were used to measure the ocular safety.

Study C-82-24 was conducted in a randomized, double-blind 3x3 Latin Square design with a 7 day washout, while Study C-81-25 was carried out using a randomized double-blind cross-over design with a 3 day washout. In Study C-82-24 (2 investigators), pulse rates were taken at baseline, and 2, 4, 6, 8, and 10 minutes during exercise; blood pressures were measured at baseline and 2, 4, 6, 8, and 10 minutes during exercise (Investigator Atkins) and at baseline and 5, and 10 minutes during exercise (Investigator Pugh).

In Study C-81-25, the primary variables (safety) were FEV_1, FVC, flow rate, blood pressure, pulse and respiratory rate, which were taken at baseline, and 15, 30, 60, 120, 180, and 240 minutes after drug instillation.

The efficacy variable IOP (change from baseline) was analyzed using a repeated-measures design analysis of variance in Study 79-E-11, while in Study 79-E-23, it was evaluated cross-sectionally using an analysis of variance. The systemic and ocular safety data were analyzed similarly.

The safety data of both C-82-24 and C-81-25 were analyzed using analysis of variance.

III. Results reported by the sponsor

In Study 79-E-11, 6 investigators enrolled 102 patients (49 on Betaxolol, 53 on placebo) of which 91 patients (44 and 47 respectively) were efficacy evaluable. The Betaxolol patients obtained a significantly greater average decrease in IOP from baseline than their placebo counterparts ($p < .001$) at each visit of the 6 week study (an average reduction of at least 5 mmHg on Betaxolol vs. less than 1 mmHg on placebo). For systemic and ocular safety, no statistically significant difference between treatment groups was found.

In Study 79-E-23, 11 investigators recruited 269 patients (132 on Betaxolol, 137 on Timolol) of which 188 patients (93 and 95 respectively) were efficacy evaluable. The data revealed that Timolol patients obtained consistently greater average decreases in IOP than their Betaxolol counterparts at each visit of the 26 week study. However, the differences were not statistically significant at the 5% level.

For systemic and ocular safety, Timolol patients experienced a greater drop in pulse rate than Betaxolol patients; Betaxolol patients obtained a greater decrease in MAP than Timolol patients; and Betaxolol patients had a decrease in pupil diameter while Timolol patients showed an increase from baseline.

Again, no statistically significant differences between treatment groups were found for each of these 4 safety variables, except pulse rate at week 1. Details are given in Table 7.

Table 2: Summary of Efficacy and Systemic and Ocular Safety

Variables	Protocol 79-E-11			Protocol 79-E-23		
	Betaxolol 0.25%	Placebo	P-value	Betaxolol 0.5%	Timolol 0.5%	P-value
IOP (mmHg)						
Baseline	29.51/44	29.37/47	.937	28.81/59	28.59/71	.691
Week 1	- 5.18/40	- 0.67/45	< .001	- 7.09/54	- 8.68/67	.098
Week 2	- 5.22/42	- 0.43/47	< .001	- 8.15/56	- 8.74/70	.438
Week 4	- 5.46/44	- 0.08/45	< .001	- 8.33/56	- 9.53/66	.103
Week 6	- 5.46/42	- 0.46/46	< .001	- 8.11/56	- 9.09/67	.238
Week 8				- 8.30/55	- 9.63/68	.058
Week 17				- 7.83/56	- 9.07/69	.085
Week 26				- 6.84/56	- 7.65/70	.532
Pulse (beats/minute)						
Baseline	74.57/47	75.61/46	.768	75.58/36	76.00/39	.735
Week 1	- 0.53/43	- 1.18/44	.738	.42/33	- 3.94/36	.009
Week 2	0.38/45	- 2.35/46	.127	- 2.17/32	- 4.67/39	.155
Week 4	- 0.60/47	- 1.36/44	.707	- 1.50/34	- 4.72/36	.301
Week 6	- 1.33/45	- 1.61/44	.894	.30/33	- 5.25/36	.051
Week 8				- 0.71/34	- 5.46/37	.094
Week 17				- 2.06/36	- 4.08/39	.257
Week 26				- 1.71/35	- 5.41/39	.089
MAP (mmHg)						
Baseline	103.37/47	102.60/46	.971	98.17/36	97.32/39	.920
Week 1	- 1.24/43	- 1.71/44	.803	- 2.80/33	- 1.44/36	.792
Week 2	- 2.34/45	- 3.15/46	.678	- 2.17/35	- 0.72/39	732
Week 4	- 7.28/47	- 1.36/43	.160	- 1.30/34	- 0.14/36	.761
Week 6	- 1.59/45	- 2.80/44	.611	- 1.02/33	- 0.57/36	.660
Week 8				- 3.68/34	- 2.10/37	.698
Week 17				- 2.38/36	- 0.38/39	.483
Week 26				- 2.76/35	- 0.20/39	.310

Table 2 (Continued)

Variables	Protocol 79-E-11 Betaxolol 0.25%	Placebo	P-value	Protocol 79-E-23 Betaxolol 0.5%	Timolol 0.5%	P-value
Pupil Diameter (mm)						
Baseline	3.44/43	3.38/47	.769	3.46/65	3.24/80	.014
Week 1	- 0.07/43	- 0.01/44	.670	- 0.09/60	0.02/72	.342
Week 2	0.05/46	- 0.02/47	.621	- 0.10/62	0.[illegible]	.454
Week 4	- 0.02/48	- 0.04/45	.894	- 0.03/63	0.1[illegible]	.829
Week 6	- 0.12/45	0.06/45	.226	- 0.14/61	0.1[illegible]	.473
Week 8				- 0.06/51	0.12/78	.355
Week 17				- 0.01/63	0.[illegible]/77	.8[illegible]
Week 26				- 0.26/5[illegible]	0.02/78	.59[illegible]
Basal Tear Secretion (mm)						
Baseline	15.56/44	14.72/47	.232	16.[illegible]/94	17.[illegible]	.[illegible]
Week 6	0.94/44	- 0.43/47	.429			
Week 26				0.24/94	0.68[illegible]	.89[illegible]

Note: (1) Numbers separated by "/" are mean and sample size respectively. All measurements are changes from baseline.
(2) All entries are taken from volume 1.5 except the p-values for Protocol 79-E-[illegible] which were calculated by this reviewer for each weekly change from baseline.

In Study C-82-24, 2 investigators enrolled 24 healthy volunteers (12 subjects each) to evaluate the effect of Betaxolol 1.0% on pulse rate and blood pressure during a 10-minute treadmill test in comparison with Timolol 0.5% and placebo.

The data showed that mean pulse rates were not significantly different when patients were on Betaxolol than when they were given placebo during 4-10 minutes of exercise. However, patients experienced a significantly lower pulse rate (an average difference of at least 6 beats/minute) on Timolol than on placebo during 4-10 minutes of treadmill testing. In terms of blood pressures (MAP), no statistically significant difference was found among treatments.

In Study C-81-25, the effect of Betaxolol 1.0% Solution was evaluated in comparison with Timolol 0.5% and placebo in 9 patients with reactive airway disease as evidenced by at least a 15% reduction in FEV_1. The data showed that patients experienced a significantly greater average decrease from baseline in FEV_1 on Timolol (approximately -14% to -27%) than on Betaxolol (-6% to +7%) or placebo (-0.7% to + 10%) during the period 30-240 minutes post drug instillation. After 240 minutes (post drug instillation), a beta-stimulant (Isoproterenol) was administered. An analysis of changes in FEV_1 from baseline during the post stimulant period showed that patients obtained significantly less FEV_1 recovery on Timolol than on Betaxolol or placebo (Mean change of 0.16%, 0.48%, and 0.43% for Timolol, Betaxolol and placebo respectively). However, no statistically significant difference among treatment groups was found in respiratory rate or MAP.

Among a total of 1117 patients or normal subjects enrolled in 17 protocols, the most frequently reported treatment-related side effects included discomfort (24.9% on Betaxolol vs. 15.8% on Timolol), tearing (4.6% vs. 7.9%), photophobia (1.2% vs. 4.0%), acute pain (1.4% vs. 1.5%), inflammation (0.7% vs. 5.0%), itching (0.2% vs. 2.0%), erythema (0.6% vs. 2.5%), foreign body sensation (0.2% vs. 2.0%), and corneal sensitivity (0.2% vs. 2.0%). Unfortunately, the sponsor did not indicate the number of patients (or subjects) in each treatment group; therefore, a statistical comparison of these incidence rates can not be carried out.

IV. Reviewer's Comments

Several deficiencies in data handling and analysis are noted below:

(1) In Studies 79-E-11 and 79-E-23, IOP was measured on both eyes, but the statistical analysis was performed based on the average of two eyes. A large percentage of patients had missing values on one eye (e.g., 30% on Betaxolol vs. 45% on Timolol for Investigator Caldwell in Protocol 79-E-23, and 33.3% on Betaxolol vs. 30.0% on placebo for Investigator Kaufman in Protocol 79-E-11). A disparity in proportions of missing values between treatment groups may make it difficult to justify the homogeneity assumption in the analysis of variance model used by the sponsor. However, based on a quick check of the data listings, the disparity may not alter the test results, especially since the F-test is generally very robust.

(2) For those patients who discontinued due to treatment failure, the last observed value was used for all subsequent follow-up periods in the statistical analysis of efficacy and systemic and ocular safety data. To examine the impact of drop-outs on efficacy and safety results, an analysis should also be carried out at each visit using only those patients who returned for follow-up. The substitution of last visit values used by the sponsor assumes that the condition of patients at the time of dropping out would remain constant throughout the study. If a longer duration of therapy improves response, this procedure would tend to repeatedly bias results against the group which has a higher percent of early drop-outs due to treatment failure, particularly when the data was analyzed cross-sectionally (i.e., at each visit) as in Study 79-E-23. In that study, efficacy results may be biased in favor of Timolol because the percent of early withdrawals due to inadequate control of IOP was 6.5% on Betaxolol vs. 1.1% on Timolol.

(3) Protocol C-81-25 was conducted using a cross-over design. However, the pulmonary function data were not analyzed accordingly.

(4) The pulmonary function of patients in Study C-81-25 was measured at baseline, 15, 30, 60, 120, 180, and 240 minutes after drug instillation and was analyzed at each observation time. An analysis of area under the curve (of repeated pulmonary function tests) is recommended to test for differences between treatments in their effects on pulmonary function over the entire observation period.

(5) Adverse reactions were tabulated but not statistically analyzed, as indicated on page 7 or this review.

(6) The sponosor did not provide power calculations to judge whether or not Protocol 79-E-23 involved sufficient numbers of patients to rule out clinically important differences between the effects of Betaxolol and Timolol. However, assuming that the standard deviation of IOP is 3.5 mmHg, as observed, this reviewer finds that the sample size of 56 patients per group provides adequate power (roughly 30%) to detect a mean difference of 2 mmHg in IOP at the 5% significance level.

The correction of these deficiencies would be helpful. However, this reviewer does not believe that efficacy conclusions will be altered by any additional or alternative analyses.

V. Conclusion (which may be conveyed to the sponsor)

The data from Study 79-E-11 demonstrated that Betaxolol 0.25% significantly reduced IOP as compared to placebo in patients with glaucoma or ocular hypertension. In Study 79-E-23, Timolol (0.5%) produced consistently greater average reductions in IOP than Betaxolol (0.5%) during the 26-week follow-up period, but the differences (approximately 1-2 mmHg) failed to reach statistical significance at the 5% level.

In terms of systemic safety, Betaxolol and placebo were statistically comparable in their effects on pulse rate and MAP (Study 79-E-11); as compared to Timolol, Betaxolol patients showed a smaller reduction in pulse and a

greater reduction in MAP (Study 79-[illegible]). In terms of ocular safety, there were no significant differences in pupil diameter and basal tear secretion between groups treated with Betaxolol and either placebo (Study 79-E-11) or Timolol (Study 79-E-23).

In Study C-82-24, no significant differences in pulse rate or MAP were detected between Betaxolol 1.0% and placebo during treadmill exercises. Patients showed smaller percent reductions from baseline in FEV_1 on Betaxolol (-6% to +7%) than on Timolol (-14% to -27%) during a 4 hour period following drug instillation.

Side effect data pooled over [illegible] protocols indicated a somewhat higher rate of ocular discomfort with use of Betaxolol as compared to Timolol (24.9% vs. [illegible]). Other symptoms occurred in fewer than 8% of the subjects (e.g. photophobia, inflammation, itching and erythema) and were slightly more common [illegible] Timolol. These results are difficult to interpret because of the variety of protocols combined.

[illegible signature]

Kao Sh[illegible] Huang, Ph.D.
Mathematical Statistician