PRODUCT MONOGRAPH

SANDOZ BETAXOLOL
(Betaxolol Ophthalmic Solution USP)

0.5%

Antiglaucoma Agent (Ophthalmic)

Sandoz Canada Inc
145 Jules-Léger St
Boucherville PQ
J4B 7K8

Date of Preparation
July 29, 2005

Control # 099927

PRODUCT MONOGRAPH

SANDOZ BETAXOLOL

Betaxolol Ophthalmic Solution USP

0.5% w/v (as base)

THERAPEUTIC CLASSIFICATION

Antiglaucoma Agent (Ophthalmic)

ACTIONS AND CLINICAL PHARMACOLOGY

Betaxolol is a cardioselective (β_1-adrenergic) receptor blocking agent. It does not have significant membrane-stabilizing (local anesthetic) activity and is devoid of intrinsic sympathomimetic action.

Ocular
When instilled in the eye, betaxolol reduces elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. When used as a solution, the onset of action occurs within 30 minutes and the maximal effect is usually attained approximately two hours after instillation.

A single dose provides a 12-hour reduction in intraocular pressure (IOP) and twice daily administration maintains the IOP below 22 mm Hg in most patients.

Betaxolol has no effect on pupil size or accommodation.

Systemic
Ophthalmic betaxolol is virtually devoid of systemic effects. Following oral administration, the elimination half-life of betaxolol is 14 to 22 hours, and it is metabolized mainly to inactive substances which are excreted in the urine. Although betaxolol is absorbed systemically, ophthalmic doses do not ordinarily produce pharmacologically active tissue levels and thus, despite its cardioselective beta-blocking activity, it has minimal, if any, effect on heart rate or blood pressure.

Betaxolol has a low affinity for β_2-adrenergic receptors, and ophthalmic doses have no significant effect on pulmonary function as measured by forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC. Ophthalmic doses do not inhibit the effect of isoproterenol, a β-adrenergic stimulant, on pulmonary function. Therefore, ophthalmic betaxolol may be used in the treatment of patients with glaucoma or ocular hypertension who have coexisting reactive airway disease.

INDICATIONS

SANDOZ BETAXOLOL (Betaxolol Ophthalmic Solution USP 0.5%) is indicated for lowering intraocular pressure in the treatment of ocular hypertension or chronic open-angle glaucoma. It may be used alone or in combination with other IOP-lowering medication.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

Although ophthalmic betaxolol has minimal systemic effects, as with all β-adrenergic blocking agents, it should not be used in patients with sinus bradycardia, atrioventricular block greater than first degree, cardiogenic shock or patients with overt cardiac failure.

PRECAUTIONS

General

Patients who are receiving a β-adrenergic blocking agent orally and ophthalmic betaxolol should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta-blockade.

Although ophthalmic betaxolol solution has demonstrated a low potential for systemic effects, it should be used with caution in patients with bradycardia and those with diabetes (especially labile diabetes) because of possible masking of hypoglycemia. Consideration should be given to the gradual withdrawal of all β-adrenergic blocking agents in patients suspected of developing thyrotoxicosis, and also prior to general anesthesia, because of the reduced ability of the heart to respond to β-adrenergically mediated sympathetic reflex stimuli (**see Drug Interactions**).

Betaxolol, 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.

In patients with angle-closure glaucoma, the immediate treatment objective is to reopen the angle by constriction of the pupil with a miotic agent. Betaxolol hydrochloride has no effect on the pupil; therefore, ophthalmic betaxolol 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 ophthalmic betaxolol after prolonged therapy has been reported in some patients. However, in one long-term study in which 250 patients treated with betaxolol ophthalmic solution have been followed for up to three years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

Drug Interactions

Although ophthalmic betaxolol used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving oral β-adrenergic blocking drugs, or catecholamine-depleting drugs such as reserpine, because of possible additive effects. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs.

Use in pregnancy
There have been no adequate and well-controlled studies in pregnant women. Because animal reproduction 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 betaxolol hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ophthalmic betaxolol 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 three years of patient experience with betaxolol hydrochloride ophthalmic preparations.

Ocular
Betaxolol hydrochloride ophthalmic preparations have been well tolerated. Discomfort of short duration may be experienced by some patients upon instillation, and occasional tearing has been reported. 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 betaxolol hydrochloride ophthalmic preparations have been reported rarely (e.g., CNS: insomnia and depressive neurosis).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

SYMPTOMS
No data is available on overdosage in humans. However, anticipated symptoms include symptomatic bradycardia, hypotension, bronchospasm, acute cardiac failure and heart block (second or third degree).

A 10 mL container of SANDOZ BETAXOLOL, Betaxolol Ophthalmic Solution USP 0.5%, would contain 50 mg of betaxolol. Betaxolol hydrochloride at 40 mg BID is reported to be an effective and safe systemic dosage for hypertension. Thus, an individual would ingest an amount of betaxolol from one container which is less than the maximum daily oral dose of betaxolol hydrochloride.

Since the oral LD_{50} in animals ranged from 350 to 1,050 mg/kg, a 10 kg child would only receive 5.0 mg/kg if the child ingested 10 mL of the 0.5% solution. An acute toxic response is thus extremely remote.

TREATMENT
Should an overdose occur the following is suggested:

Ocular:

- Flush eye with lukewarm tap water.

Systemic:

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

DOSAGE AND ADMINISTRATION

The usual dose is one drop SANDOZ BETAXOLOL, Betaxolol Ophthalmic Solution USP 0.5%, in the affected eye(s) twice daily. In some patients, the intraocular pressure lowering response may require a few weeks to stabilize. Clinical follow-up should include a determination of the intraocular pressure during the first month of treatment. Thereafter, intraocular pressures should be determined on an individual basis at the judgment of the physician.

When a patient is transferred from a single antiglaucoma agent, continue the agent already used and add one drop of SANDOZ BETAXOLOL, Betaxolol Ophthalmic Solution USP 0.5%, in the affected eye(s) twice a day. On the following day, discontinue the previous antiglaucoma agent completely and continue with the SANDOZ BETAXOLOL, Betaxolol Ophthalmic Solution USP 0.5%.

Because of diurnal variation 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 pressure of less than 22 mm Hg 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.

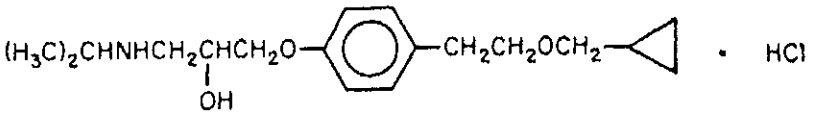
When a patient is transferred from several concomitantly administered antiglaucoma agents, individualization is required. Adjustment should involve one agent at a time made at intervals of not less than one week. A recommended approach is to continue the agents being used and add one drop of **SANDOZ BETAXOLOL**, Betaxolol Ophthalmic Solution USP 0.5%, in the affected eye(s) twice a day. On the following day, discontinue one of the other antiglaucoma agents. The remaining antiglaucoma 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 antiglaucoma agents.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCES

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

Structural Formula:



Empirical Formula:	$C_{18}H_{29}NO_3 \cdot HCl$
MW:	343.89
Physical Form:	White crystalline powder.
Solubility:	Approximately 35% in water.
pKa:	9.34
pH:	A 1% aqueous solution has a pH of 6.4.
Partition Coefficient:	3.5 (octanol: water)
Permeability Coefficient:	3.5×10^{-5} cm/sec
Melting Range:	113-117°C

COMPOSITION

SANDOZ BETAXOLOL, Betaxolol Ophthalmic Solution USP, is a sterile, isotonic aqueous solution containing betaxolol 0.5% (as 0.56% betaxolol hydrochloride) with benzalkonium chloride (as preservative), disodium edetate, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH) and water for injection.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15□ and 30□C. Discard solution within 28 days from opening.

SPECIAL INSTRUCTIONS

Patients should be instructed to avoid contamination of the dropper tip.

AVAILABILITY OF DOSAGE FORMS

SANDOZ BETAXOLOL, Betaxolol Ophthalmic Solution USP 0.5%, is supplied in plastic ophthalmic dispensers containing 5 mL, and 10 mL.

ANIMAL PHARMACOLOGY

The adrenergic receptors associated with mydriasis in man and the other mammalian species are classified as of the alpha type. Thus, it is not to be expected that beta-blockers cause a significant change in pupil size. The pupillary activity of betaxolol hydrochloride was studied in albino rabbits by instilling drops of solutions containing 0, 0.125%, 0.25%, 0.5%, or 1.0% betaxolol hydrochloride, or 0.5% proparacaine into the cul-de-sac and measuring the pupillary diameter before and at 3 hours after treatment. No change in pupil size was seen.

Pharmacokinetics

The ocular bioavailability of (^{3}H[G])-RS-betaxolol hydrochloride (0.5% ophthalmic solution) has been evaluated after administration of a 50 microliter dose in the eyes of healthy New Zealand albino rabbits. Six rabbits were used at each time interval of 5, 15, 30, 45, 60, 120, 240 and 360 minutes. One rabbit was dosed with its own positive nonradioactive control, and one rabbit was also dosed with its respective vehicle control. At the prescribed time, each rabbit was sacrificed, and samples were taken of the aqueous humour, cornea, iris and lens tissues, using appropriate techniques. The following results were obtained for Peak Time (TP_c) and Peak Concentrations (P_c) in the tissues.

	TP_c(hours)	Pc	
Aqueous humour	0.5	7.16	□g/mL
Cornea	0.5	178.45	□g/g
Iris-ciliary body	0.75	12.17	□g/g
Lens	0.5	0.86	□g/g

Due to the high lipophilicity of this compound and the rapid permeation into corneal tissue, it appears possible that the rapid de-equilibration/equilibration at the corneal surface allows high concentrations of the drug to enter the ocular tissue.

CLINICAL PHARMACOLOGY

Glaucoma is the name of a group of diseases characterized by an elevated intraocular pressure (IOP) associated with optic nerve head damage and with consequent loss of visual field. On a statistical basis, the prognosis for the preservation of visual field in an eye with elevated IOP is inversely related to the level of IOP sustained by that eye. Thus, to improve the chances for slowing the progressive loss of visual field, a goal of glaucoma therapy is to reduce the IOP to a level within a range tolerated by the eye. Present medical therapy of glaucoma involves reduction of IOP by any of a wide variety of drugs.

The mechanism of ocular hypotensive action of betaxolol in eyes with normal or elevated IOP appears to be reduction of aqueous production, as demonstrated by tonography and aqueous fluorophotometry. The onset of action when used as a solution can generally be noted within 30 minutes and the maximal effect can usually be detected two hours after topical administration. Although the time of onset of action and the time of maximal effect for the suspension have not been determined, studies in rabbits indicate that the concentration of betaxolol in the aqueous humour appears to increase at the same rate following instillation of either the solution or the suspension. A single dose provides a 12-hour reduction in intraocular pressure. Clinical observation of glaucoma patients treated with ophthalmic betaxolol solution for up to three years shows that the intraocular pressure lowering effect is well maintained.

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

Ophthalmic betaxolol solution has also been used successfully in glaucoma patients who have undergone a laser trabeculoplasty and have needed additional long-term ocular hypotensive therapy. It has been well-tolerated in glaucoma patients wearing hard or soft contact lenses and in aphakic patients.

Ophthalmic betaxolol 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 ophthalmic betaxolol. Thus, patients with central lenticular opacities avoid the visual impairment caused by a constricted pupil.

The mode of action of beta-blockers in reducing IOP has not been fully elucidated; however, available studies indicate the decrease in IOP results from a reduction in the rate of formation of aqueous humour.

Cardioselectivity, intrinsic sympathomimetic activity and membrane stabilizing activity, properties that have been used to classify beta-blockers into several categories, do not appear to be major determinants of the IOP- reducing activity of these drugs judging from the published results of clinical trials with them. However, the degree to which such ancillary properties are possessed will influence the degree to which side effects will occur. Non-selective beta-blockers at ophthalmic doses cause a significant incidence of systemic side effects, particularly cardiopulmonary effects. Consequently, non-selective beta-blockers are contraindicated in patients with pulmonary disease. In contrast, a cardioselective beta-blocker should be less apt to produce bronchoconstriction, and this has been confirmed in studies in patients with reactive airway disease using either ophthalmic or oral doses of betaxolol.

Both bradycardia and bronchospasm have been reported to occur with topical ocular use of timolol, which is a non-selective beta-blocker without intrinsic sympathomimetic activity. Betaxolol hydrochloride is a cardioselective beta-blocker lacking intrinsic sympathomimetic activity with very weak local anesthestic properties.

Ophthalmic betaxolol solution (one drop in each eye) at twice the therapeutic dosage was compared to timolol and placebo in a three-way masked crossover study challenging patient reactive airway disease. Betaxolol hydrochloride at twice the clinical concentration 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/FVC. Additionally, the action of isoproterenol, a beta stimulant, administered at the end of the study was not inhibited by ophthalmic betaxolol hydrochloride.

In contrast, ophthalmic timolol significantly decreased these pulmonary functions; the measurements subsequent to baseline were significantly ($P<0.05$) different from betaxolol hydrochloride and placebo. Additionally, the action of isoproterenol, a β-adrenergic stimulant, administered at the end of the study, was inhibited by timolol but not by betaxolol.

FEV_1 - Percent Change From Baseline

	MEANS		
	Betaxolol 1.0% solution	Timolol 0.5% solution	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	36.1	-12.4*	42.8

* Statistically significant ($P<0.05$). Isoproterenol was inhaled at 240 minutes, and FEV_1 was measured at 270 minutes after inhalation

Paradoxically, despite its cardioselective action, ophthalmic doses of betaxolol have no significant effect on heart rate. Ophthalmic betaxolol solution (one drop in each eye) at twice the clinical concentration (1%) was compared to timolol (0.5%) solution and placebo in a

double-masked three-way crossover study in 24 normal subjects comparing ophthalmic betaxolol hydrochloride, 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. The mean heart rate for timolol at 4, 6, 8 and 10 minutes was significantly ($P<0.05$) lower than betaxolol hydrochloride or placebo.

Mean Heart Rates Following Bruce Stress Test

	TREATMENT		
Minutes	Betaxolol 1% solution	Timolol 0.5% solution	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

* Mean pulse rate significantly lower for timolol than betaxolol hydrochloride or placebo ($p<0.05$).

This study confirms that ophthalmic doses of betaxolol do not produce pharmacologically active tissue levels of the drug. Reported values for the volume of distribution of betaxolol in man range from 4.9 L/kg to 8.8 L/kg. Thus, even with complete systemic absorption of ophthalmic doses of betaxolol the concentrations of drug in body tissue will be significantly below the threshold concentration of approximately 5 ng/mL. The lack of effect of betaxolol on heart rate has been confirmed in long-term clinical trials in patients with glaucoma or ocular hypertension.

Pharmacokinetics

Betaxolol is extensively absorbed from the gastrointestinal tract following oral administration, with peak plasma levels in 2 to 4 hours and an elimination half-life of 14-22 hours. The volume of distribution of betaxolol in man is 4.9 to 8.8 L/kg, the latter figures reported following repeated oral dosage.

Betaxolol is not extensively bound to plasma protein and is excreted primarily in the urine. Although betaxolol is absorbed following ocular administration, threshold levels for systemic effects are not reached.

TOXICOLOGY

Acute Toxicity

Species/Route	**LD_{50}(mg/kg)**	**Signs of Toxicity**

Mouse, PO	482.7 (377.2-617.5)	All deaths occurred within one hour in dose/response manner.
Mouse, IV	42.6 (39.5-46.0)	All deaths occurred within one hour in dose/response manner.
Mouse, PO	920 (601-1408)	Deaths 3 min - 5 hrs. after lethal oral dose.
Mouse, IV	38 (32-44)	Deaths occurred within 0.5 - 2 minutes after lethal IV dose.
Rat, PO	1050 (946-1166)	Reduced motor activity ptosis and occasional convulsions.
Rat, IV	39 (33-46)	
Mouse, PO	350 ± 23 (m) 400 ± 30 (f)	Difficulties in movement, tremors, stereotype behaviour clonic convulsions. Death 2 - 3 min. after lethal dose.
Mouse, IV	40 ± 1.5 (m) 55 ± 2.0 (f)	Tremors, convulsive jumps, clonic convulsions. Death 1 - 2 min. after lethal dose.
Rat, PO	980 ± 95 (m) 860 ± 113 (f)	Difficulties in movement, tremors, stereotype behaviour, hypersalivation, piloerection, cyanosis. Deaths within 24 hours.
Rat, IV	28 ± 1.6 (m) 25 ± 1.5 (f)	Tremors and clonic convulsions; deaths within 10 min. in dose-related manner.

Subacute Toxicity

Species/Route	**Dosage (mg/kg/day)**	**Signs of Toxicity**
Rat, IV 4 weeks	2, 6, 15	Unsteady gait after dosing, tremor, irregular breathing, pilo-erection, half-closed eyes, tail rigidity at 15 mg/kg. Reduced body weight gain and food consumption in male rats at 15 mg/kg.
Dog, IV 4 weeks	1, 3, 6	Ataxia, salivation, subduedness, high-stepping gait at 6 mg/kg during first two weeks of dosing. Reduction in heart rate at 6 mg/kg after three weeks.

R at, PO 4 weeks	25, 50, 100 (m) 50, 100, 200 (f)	Slight increase in blood glucose and serum urea at 50 mg/kg; moderate increase in serum triglyceride at 100 mg/kg (m) slight proteinuria at 100 and 200 mg/kg (f).
Rat, PO 13 weeks(f)	100, 400	Hypersalivation at 100, 400 mg/kg; prostration at 400 mg/kg. One mortality at 400 mg/kg. Increases in serum urea and creatinine levels at both dose levels. Slight hypertrophy of adrenal glands.
Rabbit, PO 4 weeks (f)	30, 100	At 100 mg/kg, lower rate of body weight gain, moderate increase in neutrophils and slight increase in serum globulin.
Mouse, PO 4 weeks	300, 400, 600	Higher incidence of poor coat condition at 400 and 600 mg/kg; dose-related reduction in weight gain at all dose levels.

Chronic Toxicity

Species/Route	**Dosage (mg/kg/day)**	**Signs of Toxicity**
Rat, PO 26 weeks	1.2, 2.5, 25, 400	Intermittent salivation, hair loss, reduced food and water intake at 1.5, 2.5 and 25 mg/kg. At 400 mg/kg, 20% mortality, salivation, tremors, unsteady gait, slight hair loss, lower body weight gain, elevated serum enzymes, elevated liver, adrenal and kidney weights. Minor histopathological changes at 400 mg/kg.
Rat, PO 61 weeks	6, 25, 100	Reduced overall body weight gain at 100 mg/kg and at 25 mg/kg (males). Slightly increased relative adrenal weights at 100 mg/kg (males), and at 25 mg/kg and 100 mg/kg (females).
Dog, PO 26 weeks	2, 6, 20	Isolated instances of convulsions at 6 mg/kg and 20 mg/kg. Occasional head-nodding movements, vomiting and salivation at 20 mg/kg. Significant reduction in heart rate after 6 and 24 weeks (2, 6 mg/kg) and after 6, 12 and 24 weeks at 20 mg/kg.

D og, PO 52 weeks	2, 6, 20	Head nodding movements, high-stepping gait, occasional vomiting and whining after dosing at 6 and 20 mg/kg. Slight decrease in systolic pressure at 6 and 20 mg/kg; possible bradycardia at 20 mg/kg.

Carcinogenicity

Species/Route	**Dosage (mg/kg/day)**	**Signs of Toxicity**
Mouse, PO 102 weeks	6, 20, 60	Reduced weight gain at 60 mg/kg. No evidence of carcinogenicity.
Rat, PO 104 weeks	3, 12, 48	Marked reduction in body weight gain at 48 mg/kg. No evidence of carcinogenicity.

Mutagenicity

Test System	Results
Ames Salmonella/Microsome Plate Test	Negative
Mouse Lymphoma Forward Mutation Assay	Negative
SCE and Chromosome Aberration Assay	Negative
In-Vivo Malignant Transformation Assay	Negative
Ames Metabolic Activation Test	Negative
Micronucleus Test	Negative

Reproduction and Teratology

Species/Route	**Dosage (mg/kg/day**	**Findings**
Rat, PO Fertility & General Reproductive Performance	4, 32, 256	Minimal effects at 4 and 32 mg/kg; maternal and fetal toxicity at 256 mg/kg.
Rat, PO Pre-and Post-Natal Development	4, 32, 256	Minimal effects at 4 and 32 mg/kg; pronounced effects at 256 mg/kg.
Rat, PO	100, 200, 400	Embryotoxic effects at 200 and 400 mg/kg. Total

Fetal Toxicity and Teratogenicity		fetal resorption at 400 mg/kg.
Rat, PO Fetal Toxicity and Teratogenicity	4, 40, 400	No significant adverse effects at 4 and 40 mg/kg. Maternal and fetal toxicity at 400 mg/kg.
Rabbit, PO Fetal Toxicity and Teratogenicity	1, 4, 12, 36	No adverse effects on organogenesis at 1, 4 or 12 mg/kg. Reduced post-implantation survival at 36 mg/kg, but no adverse effects on morphogenesis.

M iscellaneous Studies

Species/Route	**Dosage (mg/kg/day)**	**Findings**
Rabbit-Ocular Irritation (1 day)	1.5-6 mg	Moderate conjunctival congestion and discharge, minimal cloudiness at 6 hours; minimal conjunctival congestion at 24 hours.
	15 mg	Severe conjunctival congestion and discharge, minimal swelling, flare, iritis, corneal cloudiness.
Rabbit-Ocular Irritation (30 days)	3.36-33.6 mg/kg	Minimal conjunctival congestion.
Rabbit-Ocular Irritation (1 year)	6.72 mg/day	Minimal-moderate conjunctival congestion; Minimal-moderate transient conjunctival discharge; isolated instances of minimal flare, iritis, corneal cloudiness and neovascularization.
Rabbit-Ocular Irritation (1 month)	6.72 mg/day	Minimal conjunctival congestion: transient minimal discharge.
Rat-Enzyme Induction (14 days)	30, 100 mg/kg/day	No microsomal enzyme-inducing capacity.

BIBLIOGRAPHY

1. Allen RC, Epstein DL. A double-masked clinical trial of betaxolol and timolol in glaucoma patients. ARVO Inves Ophthalmol Vis Sci 1982;22(3):40.

2. Atkins JM, Pugh BR (Jr.), Timewell RM. Cardiovascular effects of topical beta-blockers during exercise. Am J Ophthalmol 1985;99:173-5.

3. Armstrong JM, Carvero I, Fenard S. The contribution of sympathetic and parasympathetic nerve mechanisms to the control of heart rate in conscious dogs at rest and during exercises as assessed by using betaxolol and methyltropine. Br J Pharmacol 1981;73:288P-289P.

4. Barrett AM. Therapeutic applications of ß-adrenoceptor antagonists. In: Morselli PL, Kilborn JR, et al (eds.): Betaxolol and Other ß-1-Adrenoceptor Antagonists. Vol 1, L.E.R.S. Monograph Series. New York: Raven Press, 1983:65-72.

5. Beresford R, Heel RC. Betaxolol: a review of its pharmacodynamics and pharmacokinetic properties, and therapeutic efficacy in hypertension. Drugs 1986;31:6-28.

6. Berrospi AR, Leibowitz HM. Betaxolol, a new beta-adrenergic blocking agent for treatment of glaucoma. Arch Ophthalmol 1982;100:943-6.

7. Berry DP Jr, Van Buskirk EM, Shields MB. Betaxolol and timolol: a comparison of efficacy and side effects. Arch Ophthalmol 1984;102:42-5.

8. Boudot JP, Cavero I, et al. Preliminary studies on SL 75212, a new potent cardioselective ß-adrenoceptor antagonist. Br J Clin Pharmacol 1979;7:445(abstr).

9. Cohn JN. Haemodynamic effects of ß-blockers. Drugs 1983;25(suppl 2):100-2.

10. Cruickshank JM. How safe are ß-blockers? Drugs 1983;25(Suppl 2):331-40.

11. Ferrandes B, Durand A, et al. Pharmacokinetics and metabolism of betaxolol in various animal species and man. In: Morselli PL, Kilborn JR, et al (eds.): Betaxolol and Other ß-1-Adrenoceptor Antagonists. Vol 1, L.E.R.S. Monograph Series. New York: Raven Press, 1983:51-64.

12. Friedmann JC. Safety evaluation of betaxolol. In: Morselli PL, Kilborn JR, et al (eds.): Betaxolol and Other ß-1-Adrenoceptor Antagonists. Vol 1, L.E.R.S. Monograph Series. New York: Raven Press, 1983:43-50.

13. Hernandez HH, Cervantes R, Frati A, et al. Cardiovascular effects of topical glaucoma therapies in normal subjects. J Toxicol 1983;2:99-106.

14. Huckauf H. Respiratory tolerance of oral betaxolol in partially reversible obstructive airways disease. In: Morselli PL, Kilborn JR, et al (eds.): Betaxolol and Other ß-1-Adrenoceptor Antagonists. Vol 1, L.E.R.S. Monograph Series, New York: Raven Press, 1983:205-11.

15. Hugues FC, Julien D, Marche J. Influence of betaxolol HCl and atenolol on airways in chronic obstructive lung diseases: comparison with propranolol. In: Morselli PL, Kilborn JR, et al (eds.): Betaxolol and Other ß-1-Adrenoceptor Antagonists. Vol 1, L.E.R.S. Monograph Series, New York: Raven Press, 1983:195-203.

16. Manoury P. Betaxolol: Chemistry and biological profile in relation to its physico-chemical properties. In: Morselli PL, Kilborn JR, et al (eds.): Betaxolol and Other ß-1-Adrenoceptor Antagonists. Vol 1, L.E.R.S. Monograph Series, New York: Raven Press, 1983:13-19.

17. Manoury P, Langer SZ, Galzin AM, et al: Basic Sciences. In: Morselli PL, Kilborn JR, et al, (eds): Betaxolol and Other B-1-Adrenoceptor Antagonists, Vol 1, L.E.R.S. Monograph Series, New York, Raven Press, pp. 13-72, 1983.

18. Reiss GR, Brubaker RF. The mechanism of betaxolol, new ocular hypotensive agent. Ophthalmology 1983;90:1369-72.

19. Robertson JIS. State-of-the-art review: ß-blockade and the treatment of hypertension. Drugs 1983;25(Suppl 2):5-11.

20. Schoene RB, Abuan T, Ward RL, et al. Effects of betaxolol, timolol and placebo on pulmonary function in asthmatic bronchitis. Am J Ophthalmol 1984;97:86-92.

21. Shanks RG, et al. Clinical pharmacology. In: Morselli PL, Kilborn JR, et al (eds.): Betaxolol and Other ß-1-Adrenoceptor Antagonists. Vol 1, L.E.R.S. Monograph Series. New York: Raven Press, 1983:73-241.

22. Sonksen PH, Brown PM, et al. Metabolic and cardiovascular effects of betaxolol during hypoglycemia and exercise in normal volunteers. In: Morselli PL, Kilborn JR, et al (eds.): Betaxolol and Other ß-1-Adrenoceptor Antagonists. Vol 1, L.E.R.S. Monograph Series. New York: Raven Press, 1983:143-154.