CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-287

Pharmacology Review(s)

NDA #
21287

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

ITEM	YES	NO	COMMENT
1) Does this action of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	✓		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	✓		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	✓		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were submitted form the NDA.	✓		

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	✓		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie. Adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	✓		
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	✓		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	✓		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item #10 below why it is not.	✓		
10) Reasons for refusal to file:			

Reviewing Pharmacologist 1/28/03

Supervisory Pharmacologist 1/28

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Laurie McLeod
1/29/03 11:59:57 AM
PHARMACOLOGIST

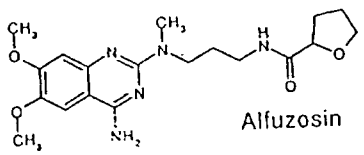
Alexander W. Jordan
1/29/03 03:02:41 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21287
Review number: memo, addendum to NDA review
Serial number/date/type of submission: original NDA, 8 December 2000
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Sanofi-Synthelabo, 6-8 Route de Rouen, ZI de Limay Porcheville, 78440 Gargenville, France
Manufacturer for drug substance: Sanofi-Synthelabo
Reviewer name: Laurie McLeod
Division name: Division Name: Division of Reproductive and Urologic Drug Products
HFD-580
Review completion date: 4 October 2001

Drug:

Trade name: Uro-xatral
Generic name: Alfuzosin hydrochloride
Code name: SL77.0499-10
Chemical name: Alfuzosin Hydrochloride; N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl) methylamino]propyl] tetrahydro-2-furancarboxamide hydrochloride
CAS registry number: 81403-68-1
Molecular formula/molecular weight: $C_{19}H_{27}N_5O_4$ HCl / 425.9
Structure:



Alfuzosin

Relevant INDs/NDAs/DMFs: IND [redacted]
Drug class: alpha-1 adrenoceptor antagonist
Indication: Benign Prostatic Hyperplasia (BPH)

Clinical formulation: 10 mg Alfuzosin hydrochloride in an extended release tablet containing silicon dioxide, ethylcellulose hydrogenated castor oil, hydroxypropylmethylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, povidone, and yellow ferric oxide

Route of administration: oral

Proposed use: one tablet per day for the treatment of the signs and symptoms of benign prostatic hyperplasia

Issue:

Final division labeling comments for this product were deferred this review cycle. The following labeling comments made by Dr. Abby Jacobs on 9/28/01 should, however, be communicated to the sponsor:

1. Overall

The pharm/tox sections should indicate when the oral studies were done by gavage to avoid the confusion caused by different multiples of the human exposure being reported for similar doses, due to the fact that dietary bioavailability is much lower than bioavailability by gavage.

2. The Pregnancy section

a. This section should follow the Carcinogenesis section, not precede it.

b. The route should be given for the rat teratogenicity studies. For rabbits, the multiples of human exposure should be given as mg/m^2 in the absence of AUC data.

3. **The Carcinogenesis section**

a. The actual doses (in mg/kg) used in the carcinogenicity studies should be given, in addition to giving the multiples of human exposure.

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/s/

Laurie McLeod
10/4/01 10:22:52 AM
PHARMACOLOGIST

Comments on labeling for NDA21-287 uroxatral (alfuzosin hydrochloride)
A. Jacobs 9/28/01 G.J 9/28/01

1. Overall

Perhaps the pharm/tox sections should indicate when the oral studies were gavage. It is confusing to see different multiples of the human exposure for similar doses, but the reason is that dietary bioavailability is much lower than bioavailability by gavage.

2. The pregnancy section

a. This section should follow the Carcinogenesis section, not precede it.

b. The route should be given for the rat teratogenicity studies. For the rabbits, the multiples of human exposure should be given as mg/m^2 in the absence of AUC data.

3. **The Carcinogenesis section**

a. The actual doses (in mg/kg) used in the carcinogenicity studies should be given, in addition to giving the multiples of human exposure.

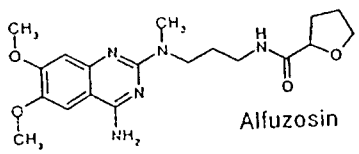
b. The statement about the adequacy of the study in female mice has been added to the labeling, as requested by the pharm/tox reviewers

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21287
Review number: 2 (previous review by A. Jordan attached)
Serial number/date/type of submission: original NDA, 8 December 2000
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Sanofi-Synthelabo, 6-8 Route de Rouen, ZI de Limay Porcheville, 78440 Gargenville, France
Manufacturer for drug substance: Sanofi-Synthelabo
Reviewer name: Laurie McLeod
Division name: Division Name: Division of Reproductive and Urologic Drug Products
HFD-580
Review completion date: 14 August 2001

Drug:

Trade name: Uro-xatral
Generic name (list alphabetically): Alfuzosin hydrochloride
Code name: SL77.0499-10
Chemical name: Alfuzosin Hydrochloride; N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl) methylamino]propyl] tetrahydro-2-furancarboxamide hydrochloride
CAS registry number: 81403-68-1
Molecular formula/molecular weight: $C_{19}H_{27}N_5O_4$ HCl / 425.9
Structure:



Alfuzosin

Relevant INDs/NDAs/DMFs: IND #
Drug class: alpha-1 adrenoceptor antagonist
Indication: Benign Prostatic Hyperplasia (BPH)

Clinical formulation: 10 mg Alfuzosin hydrochloride in an extended release tablet containing silicon dioxide, ethylcellulose hydrogenated castor oil, hydroxypropylmethylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, povidone, and yellow ferric oxide

Route of administration: oral

Proposed use: one tablet per day for the treatment of the signs and symptoms of benign prostatic hyperplasia

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

Introduction: Alfuzosin hydrochloride is a selective antagonist of post-synaptic alpha$_1$-adrenoceptors, which are located in the prostate and bladder. It therefore relaxes smooth muscle tone at the bladder outlet.

Alfuzosin hydrochloride has been tested in a variety of clinical formulations over a period of 15 years and was first marketed in Europe in 1987.

Safety evaluation:

Alfuzosin was tested for up to one year in rats (>200 times the clinical exposures) and dogs (>300 times the clinical exposures).

Sedation, palpebral ptosis, hypersalivation, hypotonicity and soft feces, due to the pharmacological actions of alfuzosin, were the primary effects. Toxic effects, such as decreased body weight gain, reduced food consumption, increased liver weight and effects on the lungs, were seen at the higher doses.

Effects on gestation length were observed at greater than 12 times the clinical exposure levels. However, no effect of teratogenicity or embryotoxicity was observed in rats at 1200 times the clinical exposure. Alfuzosin is not indicated for use in women.

No genotoxic effects were seen in a battery of tests. No treatment related tumors were observed in male or female rats or male or female mice in 2-year carcinogenicity studies, although female mice may not have been tested at the maximally tolerated dose.

Safety issues relevant to clinical use: Alfuzosin is not indicated for use in women.

Other clinically relevant issues: none

Conclusions: From a Pharmacology/Toxicology standpoint, this drug is approvable with a minor labeling change.

Communication review:

Labeling review:

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In this section, in paragraph #1, a sentence should be added after sentence #1, which reads, "The doses tested in female mice may not have constituted a maximally tolerated dose."

RECOMMENDATIONS:

Draft letter content for sponsor :

A labeling change is required in section "Carcinogenesis, Mutagenesis, and Impairment of Fertility." In paragraph #1, a sentence should be added after sentence #1, which reads, "The doses tested in female mice may not have constituted a maximally tolerated dose," since no indication of dose limiting toxicity was observed.

Future development or issues: none apparent

Reviewer signature:

Team leader signature [concurrence/non-concurrence]:

cc: Alex Jordan, Laurie McLeod, Evelyn Farinas

Memorandum of non-concurrence (if appropriate, attached):

Addendum to review (if necessary):

TABLE OF CONTENTS

PHARMACOLOGY:

See attached Review #1.

SAFETY PHARMACOLOGY:

See attached Review #1.

PHARMACOKINETICS/TOXICOKINETICS/ADME:

Species	Doses (mg/kg)	Day	Cmax		AUC 0-24	
			ng/ml	ratio	nghr/ml	ratio
Man, 10 mg	~0.14	5	16.6	-	238	-
Rat, 1 month TK study, male	5	1	36	2.2	239	1.0
	5	29	41	2.5	199	0.83
	30	1	840	50.6	4210	17.6
	30	29	890	53.6	4360	18.3
	200	1	5020	302	47200	199
	200	29	8130	490	109000	457
Rat, 1 month TK study, female	5	1	98	5.9	493	2.1
	5	29	112	6.7	447	1.9
	30	1	1830	111	7820	32.9
	30	29	2010	121	7960	33.4
	200	1	6120	368	90300	380
	200	29	12600	759	156000	657
Dog, 1 month TK study, male	5	1	2730	165	100000	42.0
	5	29	3120	188	11900	50.1
	20	1	4400	265	22900	96.4
	20	29	4370	263	36900	155
	80	1	8550	515	113000	475
	80	29	9920	597	111000	466
Dog, 1 month TK study, female	5	1	2000	120	5440	22.9
	5	29	2500	150	9930	41.7
	20	1	5270	317	24300	102
	20	29	6520	393	48800	205
	80	1	8340	502	75600	318
	80	29	9110	549	95000	399

ADME	Compound	RAT		DOG		RAT		MOUSE	
		male	female	male	female	male	female	male	female
	Dose (mg/kg)	1	1	1	1	92	92	92	92
Urine 0-24 hours	Total radioactivity	0.2	5.9	11.5	9.4	10.8	9.9	12.2	22.0
	Alfuzosin	1.7	2.2	1.1	1.2	8.4	7.1	6.2	7.4
	SL 80.0037	2.9*	2.2*	5.4*	3.8*	-	0.1*	2.6*	4.9*
	SL 80.0018	0.4*	0.2*	0.6*	3.8*	-	-	1.1*	-
	SL 80.0363	1.1	0.9	0.8	0.9	1.4	1.7	0.2	2.0
Feces 0-24 hours	Total radioactivity	82.6	50.9	83.9	88.0	77.0	77.8	70.7	64.1
	Alfuzosin	46.0	28.1	1.2	0.5	50.4	48.6	15.3	12.8
	SL 80.0037	10.8	9.5	27.7	25.9	3.9	4.0	6.9	5.9
	SL 80.0018	1.6	1.1	1.6	-	1.3	1.2	0.8	-
	SL 80.0363	13.6	7.5	30.9	35.8	17.2	19.7	36.9	38.5

Plasma	Alfuzosin, 0.5 hr	64.3	72.6	NP	NP	NP	NP	NP	NP
	Alfuzosin, 1 hr	NP	NP	NP	NP	46.5	61.8	28.2	25.7
	Alfuzosin, 2 hr	72.3	72.1	NP	NP	NP	NP	NP	NP
	Alfuzosin, 4 hr	64.4	67.0	NP	NP	77.7	82.4	22.9	37.7
	SL 80.0037, 0.5hr	15.7*	7.6*	NP	NP	NP	NP	NP	NP
	SL 80.0037, 1 hr	NP	NP	NP	NP	9.4*	6.8*	42.9*	51.0*
	SL 80.0037, 2 hr	16.6*	14.7*	NP	NP	NP	NP	NP	NP
	SL 80.0037, 4 hr	15.2*	28.0*	NP	NP	2.6*	7.1*	57.6*	39.0*
	SL 80.0018, 0.5hr	-	9.5*	NP	NP	NP	NP	NP	NP
	SL 80.0018, 1 hr	NP	NP	NP	NP	-	-	11.3*	-
	SL 80.0018, 2 hr	-	-	NP	NP	NP	NP	NP	NP
	SL 80.0018, 4 hr	4.9*	-	NP	NP	-	-	9.7*	-
	SL 80.0363, 0.5hr	14.1	7.7	NP	NP	NP	NP	NP	NP
	SL 80.0363, 1 hr	NP	NP	NP	NP	13.6	9.6	-	-
	SL 80.0363, 2 hr	11.1	12.1	NP	NP	NP	NP	NP	NP
	SL 80.0363, 4 hr	10.3	4.9	NP	NP	6.8	2.7	-	-

* as glucuronide (mainly, if not solely)
NP not performed
- not detected

In addition, see attached Review #1.

TOXICOLOGY:

Alfuzosin was tested for up to one year in rats (>200 times the clinical dose) and dogs (>300 times the clinical dose).

Sedation, palpebral ptosis, hypersalivation, hypotonicity and soft feces, due to the pharmacological actions of alfuzosin, were the primary effects. Toxic effects, such as decreased body weight gain, reduced food consumption, increased liver weight and effects on the lungs, were seen at relatively high doses.

See attached Review #1 for details.

GENETIC TOXICOLOGY:

TEST	COMMENTS
Bacterial mutagenesis	Negative
Mouse lymphoma mutagenesis	Negative
Chromosomal aberration in CHO cells	Negative
Unscheduled DNA synthesis in HSBP	Negative
Mouse micronucleus	Negative

See attached Review #1.

In addition, a new GLP Ames test was performed:

Study title: *In vitro* evaluation of the mutagenic potential of alfuzosine (SL77.0499-10) by the reverse mutation assay in *Salmonella Typhimurium* (Regulatory Ames Test).

Study no: 00-00155-EN-00
Volume #46, and page #71
Conducting laboratory and location: Synthelabo
Date of study initiation: 27 July 2000
GLP compliance: yes
QA reports: yes (x) no ( )
Drug: lot #19364
Formulation/vehicle: sterile water

Methods:

Strains/species/cell line: TA 1535, TA 1537, TA 98, TA 100 and TA 102
Doses: 0, 50, 100, 250, 500, 1000, 2500, and 5000 µg/plate with and without S-9 mix
Metabolic activation system: S-9 mix (10%) form Aroclor 1254-induced rat liver
Controls:
Vehicle: sterile water for injections
Negative controls: sterile water for injections
Positive controls: w/o metabolic activation, Na azide (2 µg/plate, TA 100, TA 1535), 2-nitrofluorene (2.5 µg/plate, TA 98), 9-aminoacridine (50 µg/plate, (TA 1537), mitomycin C (0.25 µg/plate, TA 102) and w/ metabolic activation, 2-aminoanthracene (2 µg/plate, TA 8, TA 100, TA 1535, TA 1537) (10 µg/plate, TA 102)
Exposure conditions:
Incubation and sampling times: 48 hours
Doses used in definitive study: 0, 50, 100, 250, 500, 1000, 2500, and 5000 µg/plate
Study design: both direct incorporation and preincubation methods
Analysis:
No. of replicates: 3 plates/concentration, 2 independent tests

Summary of individual study findings:

Study validity: Positive and negative controls responded as expected.
Study outcome: No genotoxicity was observed under any of the conditions tested in this assay.

Labeling recommendations: The proposed label accurately represents the data.

CARCINOGENICITY:

Study Title: 104 week oral (dietary administration) study in the mouse
or 98 week oral (dietary administration) carcinogenicity study in the mouse
Study Number: 85-00666-EN-01
Volume Numbers: 7-11
Test Facility: [redacted]

Study Date(s): 31 March 1983-5 March 1985
Date of Submission: 25 July 2000
GLP Compliance/Quality Assurance: yes
QA Report- Yes (x) No ()
Study Type: 2 year, dietary
Species/strain: Crl CD-1(ICR)BR
Number of animals per group; age at start of study: 51/sex, age 41 days, weighing 17.5-34.1 g (males) and 17.3-26.9 g (females)
Animal housing: groups of 3, by sex
Drug Lot/Batch number(s): 11 415
Drug Purity / Stability / Homogeneity: 99% pure, stability and homogeneity for the duration of the study confirmed
Doses: 0, 10, 30, and 100 mg/kg/day
- Basis of Dose Selection: A six week dose finding study was performed in B6C3F1 mice, and palpebral ptosis due to the pharmacological activity of alfuzosin was seen at 300 and 500 mg/kg/day along with increases in hematocrit and hemoglobin and extramedullary splenic hematopoiesis. The choice of mouse strain to be used for carcinogenicity testing was then changed due to lack of adequate background data in B6C3F1 mice. A four week study in Crl CD-1(ICR)BR study showed no toxicity up to 30 mg/kg/day. No higher doses were tested in that strain. Post hoc, excess mortality was seen in high dose males in the 98 week study along with a 10% increase in liver weight (without microscopic correlates). No toxicity was observed in female mice.

- Relation to Clinical Use: The low dose, when protein binding is considered, is approximately equal to the clinical exposure. The high dose in males is approximately 10 times the maximum clinical exposure expected, when protein binding is considered.
- CAC Concurrence: see attached
- Route of Administration: oral, dietary
- Frequency of Drug Administration: fresh food mixtures supplied weekly
- Dual Controls Employed: two identical
- Satellite PK or Special Study Group(s): 12 males at 0 and 12 males at 100 mg/kg/day for blood analysis on day 2, week 13, and week 26
- Unscheduled Sacrifices or Deaths:

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	10	30	100	0	0	10	30	100
% Survival at week 98	41	53	51	49	25	59	46	59	63	63

- Deviations from Original Study Protocol: none significant

- Body weights:

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	10	30	100	0	0	10	30	100
%BW change (vs cont 1)	-	-4	+4	+5	+9	-	-8	+1	-4	+11
%BW change (vs cont 2)	+4	-	+7	+9	+14		-	+9	+7	+21
%BW change (vs cont 1+2)	-	-	+5	+7	+11	-	-	+6	-	+15

- Food consumption:

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	10	30	100	0	0	10	30	100
Food consumption wk 0-4 (% increase vs cont 1+2)	-	-	-2.8	-1.4	3.2	-	-	-3.5	-0.08	3.6
Food consumption wk 0-13 (% increase vs cont 1+2)	-	-	-3.4	-0.9	2.4	-	-	-0.4	2.5	6.2
Food consumption wk 0-26 (% increase vs cont 1+2)	-	-	-4.0	-1.8	1.9	-	-	-0.8	3.7	4.9
Food consumption wk 0-98 (% increase vs cont 1+2)	-	-	-3.5	-2.3	-1.1	-	-	-2.4	2.0	2.4

- Histopathology:

Non-tumor data

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	10	30	100	0	0	10	30	100
Heart										
fibrosis	4	2	0	0	9	1	0	0	1	0
myositis	0	0	0	0	0	0	0	0	0	2
Ovary										
amyloidosis						9	6	4	5	13
Prostate										
prostatitis	2	4	1	3	7					
Uterus										
arteritis						0	0	0	1	4

Tumor data

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	10	30	100	0	0	10	30	100
Abdominal cavity										
sarcoma	0	0	0	0	0	0	0	0	0	1
histiocytic sarcoma	0	0	0	0	0	0	0	0	0	1
Adrenal										
adenoma	0	1	1	1	2	0	0	0	0	0
Bone										
fibroma	0	0	0	0	0	0	0	0	0	1
Bone marrow										
hemangiosarcoma	0	0	0	0	0	0	0	0	0	1
Harderian gland										
adenoma	0	0	0	1	0	0	0	0	1	1
Kidney										
adenoma	0	0	0	0	1	0	0	0	0	0
Liver										
adenoma	13	13	14	13	17	1	0	1	0	0

Pancreas histiocytic sarcoma	0	0	0	0	1	0	0	0	0	0
Pituitary adenoma	0	0	0	0	1	0	0	0	0	0
Skin, subcutis __adenoma __sarcoma __hemangiosarcoma	0 0 1	0 0 0	0 0 0	0 0 0	1 2 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 1
Spleen hemangiosarcoma	0	0	0	0	0	0	0	0	1	1
Uterus __adenomatous polyp __fibroma						1 1	0 0	0 0	2 0	2 2
Other tissue histiocytic sarcoma	0	0	0	0	1	0	0	0	0	0

Overall Interpretation and Evaluation

- Adequacy of the carcinogenicity studies and appropriateness of the test model: The doses were adequate in male mice based on an increase in mortality at the high dose. However, no toxicity was observed in female mice. In addition, the ratio of animal to human exposure was inadequate based on the expected 10 mg dose, even when differences in protein binding was considered in the calculations.
- Evaluation of Tumor Findings: negative tumor findings

Study Title: One hundred four week oral (dietary administration) carcinogenicity study in the rat.
Study Number: 85-00665-EN-00
Volume Numbers: 14-19
Test Facility: [redacted]

Study Date(s): 3 March 1983-25 March 1985
Date of Submission: 25 July 2000
GLP Compliance/Quality Assurance: yes
QA Report- Yes (x) No ()
Study Type: 2-year, dietary
Species/strain: Sprague-Dawley Crl:CD(SD)BR
Number of animals per group; age at start of study: 50/sex/group, aged 26 days
Animal housing: groups of 5 by sex
Drug Lot/Batch number(s): Lot: 11 415
Drug Purity / Stability / Homogeneity: 99% pure, stability and homogeneity for the duration of the study confirmed
Doses:

- Basis of Dose Selection: A four week dose finding study was performed in Crl:CD(SD)BR rats, and severe and persistent blepharospasm and marked and progressive relaxation of the vaginal musculature were seen at 300 mg/kg/day along with changes in erythrocytes, enzymes, and triglycerides, and panacinar pallor of the liver. Post hoc, a maximally tolerated dose was considered to have been reached in both sexes as indicated by a 10% decrease in body weight gain. A decrease in food consumption was dismissed by the sponsor as the cause of the decrease in body weight change because it became significant at greater than 26 weeks and

because food spillage was not increased. Increased liver weight without microscopic correlates was also seen at 100 mg/kg/day.

- Relation to Clinical Use: The high doses were 25 and 35 times the maximum clinical dose in males and females, respectively.
- CAC Concurrence: none
- Restriction Paradigm for Dietary Restriction Studies: na
- Route of Administration: oral, dietary
- Frequency of Drug Administration: continuous, with fresh food supplied weekly
- Dual Controls Employed: two identical
- Satellite PK or Special Study Group(s): 3/sex in control 1 and 9/sex in low, mid, and high dose groups (blood for pk measurements taken day2, week 26, and week 39)
- Unscheduled Sacrifices or Deaths: No treatment related effects were observed.
- Deviations from Original Study Protocol: none significant
- Body weights

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	10	30	100	0	0	10	30	100
%BW change (vs cont 1)	-	-5	-1	-5	-16	-	+3	-3	+7	-15
%BW change (vs cont 2)	+6	-	+5	+1	-11	-3	-	-6	+4	-17
%BW change (vs cont 1+2)	-	-	+2	-2	-14	-	-	-4	+5	-16

- Food consumption:

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	10	30	100	0	0	10	30	100
Food consumption wk 0-4 (% increase vs cont 1+2)	-	-	1.3	1.3	2.7	-	-	0.39	1.3	1.0
Food consumption wk 0-13 (% increase vs cont 1+2)	-	-	1.6	0.53	-0.10	-	-	2.0	1.8	0.05
Food consumption wk 0-26 (% increase vs cont 1+2)	-	-	1.7	0.31	-2.0	-	-	1.7	2.2	-0.61
Food consumption wk 0-104 (% increase vs cont 1+2)	-	-	-0.10	-0.10	-3.3	-	-	0.27	2.9	-0.82

- Histopathology:

Tumor data

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	10	30	100	0	0	10	30	100
Hemolymphoreticular										
lymphoma, histiocytic	1	1	1	1	2	0	0	1	0	2
lymphoma, mixed	0	0	0	0	2	0	0	0	0	0
Kidney										
carcinoma	0	0	0	0	1	0	0	0	0	0
Mammary gland										
adenoma	0	0	0	0	0	3	3	2	7	5
multiple adenoma	0	0	0	0	0	0	1	0	1	3
fibroadenoma	0	0	0	0	0	12	8	8	11	14
multiple carcinoma	0	0	0	0	0	0	0	0	0	1
Pituitary										
adenocarcinoma	0	0	0	0	0	0	0	0	0	2
Skin, subcutis										
dermal fibroma (foot)	0	0	0	0	1	0	0	0	0	0

Testis Leydig cell tumor	2	1	0	1	3					
Cause of morbidity/mort. hemolymph. tumor pituitary/mamm. tumor	2 0	3 0	2 0	2 0	4 0	0 6	0 7	1 6	0 4	1 9

Overall Interpretation and Evaluation

- Adequacy of the carcinogenicity studies and appropriateness of the test model: The doses were adequate based on a decrease in body weight gain. A 2-year dietary study in Crl:CD(SD)BR rats was employed using greater than 25 times the expected human exposure.
- Evaluation of Tumor Findings: negative tumor findings

Summary Conclusions and Recommendations

- Acceptability of Study(s) or Overall Testing Approach: acceptable doses in male and female rats and in male mice
- Major Tumor Findings: none
- Non-neoplastic Findings: Small, possible effects on the heart, ovary, prostate, and uterus in mice at 9-10 times human exposures.
- Potential Clinical Implications of Findings: none

Addendum/Appendix Listing

Histopathology inventory for rats and mice

Addendum 1

Histopathology Inventory for NDA#21287

Study				
Species	rat	mouse		
Adrenals	X*	X*		
Aorta				
Bone Marrow smear	X	X		
Bone (femur)	X	X		
Brain	X	X		
Cecum	X	X		
Cervix				
Colon	X	X		
Duodenum	X	X		
Epididymis	X	X		
Esophagus	X	X		
Eye	X	X		
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart	X*	X*		
Hyphophysis				
Ileum	X	X		
Injection site				
Jejunum	X	X		
Kidneys	X*	X*		
Lachrymal gland				
Larynx				
Liver	X*	X		
Lungs	X	X		
Lymph nodes, cervical				
Lymph nodes mandibular	X	X		
Lymph nodes, mesenteric	X	X		
Mammary Gland	X	X		
Nasal cavity				
Optic nerves				
Ovaries	X*	X*		
Pancreas				
Parathyroid	X	X		
Peripheral nerve				
Pharynx				
Pituitary	X*	X*		
Prostate	X	X		
Rectum				
Salivary gland	X	X		
Sciatic nerve				
Seminal vesicles	X	X		
Skeletal muscle				
Skin	X	X		
Spinal cord	X	X		
Spleen	X*	X*		
Sternum	X	X		
Stomach	X	X		
Testes	X*	X*		
Thymus	X	X		
Thyroid	X*	X*		
Urinary bladder	X	X		
Uterus	X	X		
Vagina				
Zymbal gland				

* organ weight obtained

Pharmacokinetics:

Human	N	C_{max} (ng/ml)(range)	AUC_{0-24} (nghr/ml)(range)
10 mg, Study 1	18	16.6±6.0	238±74
10 mg, Study 2	24	11.4±4.7	161±58
10 mg, Study 1+2	42	13.6±5.6	194±75
15 mg	10	22.0±7.9	360±122

PK Ratios	Human dose (mg)	Human AUC_{0-24} (nghr/ml)	Animal high dose (mg/kg/day)	Animal AUC_{0-24} (nghr/ml)	Ratio (animal/ human)	Ratio (considering protein binding)
Male rat	10	238	100	8896	37.4	nd
Female rat	10	238	100	12535	52.7	nd
Male mouse	10	238	100	1545	6.5	15.1
Female mouse	10	238	100	1338	5.6	13.4
Male rat	15	360	100	8896	24.7	nd
Female rat	15	360	100	12535	34.8	nd
Male mouse	15	360	100	1545	4.3	10.3
Female mouse	15	360	100	1338	3.7	8.8

Protein binding	Human	Rat	Mouse
95-00741-EN-00		61-63%	44-47%
85-00886-EN-00	90%		
FSRFU-LPR0863-EN-E01	82%	82%	57%

Labeling Recommendations:

In paragraph #1 of the proposed label, a sentence should be added after sentence #1, which reads, "The doses tested in female mice may not have constituted a maximally tolerated dose."

Addendum/appendix listing: CAC report:

Executive CAC
Date of Meeting: 24 October, 2000

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Abby Jacobs, Ph.D., HFD-540, Alternate Member
Alex Jordan, Ph.D., HFD-580, Team Leader
Laurie McLeod, Ph.D., HFD-580, Reviewer

Author of Draft: Laurie McLeod

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND # xxxxx
Drug Name: Alfuzosin
Sponsor: Sanofi-Synthelabo

Background: Alfuzosin is an alpha-1 adrenoceptor antagonist approved in Europe and being studied in the United States for use in benign prostatic hyperplasia. It was negative for genotoxicity in a standard battery of assays.

Mouse Carcinogenicity Study and Mouse Dose Selection

A six week dose finding study was performed in B6C3F1 mice. Palpebral ptosis due to the pharmacological activity of alfuzosin was seen at 300 and 500 mg/kg/day along with increases in hematocrit and hemoglobin and extramedullary splenic hematopoiesis. The choice of mouse strain to be used for carcinogenicity testing was then changed due to lack of adequate background data in B6C3F1 mice. A four week study in Crl CD-1(ICR)BR study showed no toxicity up to 30 mg/kg/day. No higher doses were tested in that strain.

The dose groups chosen for the carcinogenicity study were 51 mice / sex of 0, 0, 10, 30, and 100 mg/kg/day.

In the carcinogenicity study, excess mortality was seen in high dose males along with a 10% increase in liver weight (without microscopic correlates). No toxicity was observed in female mice. The high doses were 10 and 9 times the maximum clinical dose in males and females, respectively, when protein binding was considered in the calculations.

Rat Carcinogenicity Study and Rat Dose Selection

A four week dose finding study was performed in Crl:CD(SD)BR rats, and severe and persistent blepharospasm and marked and progressive relaxation of the vaginal musculature were seen at 300 mg/kg/day along with changes in erythrocytes, enzymes, and triglycerides, and panacinar pallor of the liver.

The dose groups chosen for the carcinogenicity study were 50 rats / sex of 0, 0, 10, 30, and 100 mg/kg/day.

In the carcinogenicity study, a maximally tolerated dose was considered by the sponsor to have been reached in both sexes as indicated by a 10% decrease in body weight gain. A decrease in food consumption was dismissed by the sponsor as the cause of the decrease in body weight change because it became significant at greater than 26 weeks and because food spillage was not increased. Increased liver weight without microscopic correlates was also seen at 100 mg/kg/day. The high doses were 25 and 35 times the maximum clinical dose in males and females, respectively.

Executive CAC Recommendations and Conclusions :

Mouse:

*The Committee felt that the male mice were tested at an adequate dose, but that inadequate data was given to support the female mouse dose selection

* The Committee felt that there were few or no findings, pending statistical analysis of the data.

*The label should say that the data might not adequately measure the carcinogenic potential in female mice because inadequate data was given to support the female mouse dose selection. Any tumor findings
would, none the less, be reported..

Rat:

*The Committee felt that the doses were adequate, based on a greater than 25 fold AUC ratio.

*The Committee agreed that there were no tumor findings, pending statistical analysis of the data.

Other comments and responses:
Mouse:

*The Committee felt that there were probably no findings, but recommended adding a row in the table for tabulated benign hemangiomas plus hemangiosarcomas and that the statistician be asked to look for significance in all combinations.

Tumor data

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	0	10	30	100	0	0	10	30	100
Bone marrow hemangiosarcoma	0	0	0	0	0	0	0	0	1	1
Bone, sternum hemangiosarcoma	0	0	0	0	0	0	0	0	1	0
Skin, subcutis hemangiosarcoma	1	0	0	0	0	0	0	0	1	1
Spleen hemangiosarcoma	0	0	0	0	0	0	0	0	1	1
Kidney hemangioma	0	0	0	0	0	0	0	0	1	0
Liver hemangioma	1	0	0	0	0	0	0	0	0	0
hemangiosarcoma	0	0	0	0	0	0	0	0	1	0
Mesenteric lymph node hemangioma	0	0	1	0	0	0	0	0	0	0
Total hemangiomas	1	0	1	0	0	0	0	0	1	0
Total hemangiosarcomas	1	0	0	0	0	0	0	0	5	3
Total hemangiomas plus hemangiosarcomas	2	0	1	0	0	0	0	0	6	3
Number of animals with hemangioma or hemangiosarcoma	2	0	1	0	0	0	0	0	3	1

*The committee requested copies of the histopathology tables.

Rat:

*The Committee felt that there were probably no findings, but recommended adding a table for tabulated benign hemangiomas, hemangiosarcomas, and hemangiomas plus hemangiosarcomas and requested that the statistician be asked to look for significance in all combinations.
Reponse: There was no increase in hemangiomas or hemangiosarcomas in any treatment group.

*The committee requested copies of the histopathology tables.

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
/Division File, HFD-580
/Alex Jordan, Team leader, HFD-580
/Laurie McLeod, Reviewer, HFD-580
/Adele Seifried, HFD-024
/ Evelyn Farinas, HFD-580

REPRODUCTIVE TOXICOLOGY:

See attached Review #1 for details.

Labeling recommendations: The proposed label accurately represents the data.

SPECIAL TOXICOLOGY:

Study title: Alfuzosin (SL77.0499-10): Effects on the action potential of piglet Purkinje fibres.

Key study findings: A no-effect dose level was calculated to be about 0.1 µM (42.6 ng/ml) or about 2.6 times the expected clinical blood level. The lowest dose at which an effect was seen was 1 µM or about 26 times the clinical blood level.

Study no: FIP0020
Four-month safety update, volume #25, and page #45
Conducting laboratory and location: Sanofi-synthelabo, Département de Pharmacologie Générale, 10, rue des Carrières, BP248, 92504 Rueil-Malmaison, France
Date of study initiation: 10 July 2000
GLP compliance: yes
QA reports: yes (x) no ( ):
Drug: batch # 0400.1A.02, 99.5% pure
Formulation/vehicle: Tyrode's solution

Methods: Hearts were from male [redacted] piglets, 2.9-3.2 kg. Experiments were carried out on 6 fibers from 6 different piglets using the glass microelectrode technique. Resting potential (RP), action potential amplitude (APA), action potential duration at 0 mV, 50% and 90% repolarization (APD_0, APD_{50}, APD_{90}, respectively), and the maximum rate of depolarization (dV/dt_{max}) were measured after a 30 minute period of superfusion, at 1 Hz and 0.25 Hz. Early afterdepolarizations (EADs) and action potential shapes were qualitatively analyzed.

Dosing: 0, 0.01, 0.1, 1.0, 10, and 30 µM

Results:

Effect of alfuzosin on the electrophysiological parameters for the action potential in piglet Purkinje fibers at 1 Hz

	Control	0.01 µM	0.1 µM	1 µM	10 µM	30 µM	washout
RP (mV)	-86.8	-87.5	-87.5	-87.8	-87.3	-87.5	-88.1
APA (mV)	132.0	131.9	131.6	131.8	130.9	128.9***	130.4
APD_0 (msec)	271.6	258.2	253.3	248.8	177.1***	73.7***	214.8
APD_{50} (msec)	348.6	340.7	342.9	348.4	336.1	273.0***	363.2
APD_{90} (msec)	399.8	391.4	392.9	401.0	403.2	367.8***	425.3
DV/dt_{max} (V/sec)	906.8	895.5	873.8	865.7	822.4*	749.3***	803.3

Effect of alfuzosin on the electrophysiological parameters for the action potential in piglet Purkinje fibers at .25 Hz*							
	Control	0.01 μM	0.1 μM	1 μM	10 μM	30 μM	washout
APD_{50} (msec)	~520	~490	~520	~560	~660	~680	~740
APD_{90} (msec)	~560	~530	~560	~600	~730.	~780	~810

*estimated from Sponsor's graph

Summary of individual study findings:

At 1 Hz, Alfuzosin had no effect on any action potential parameter at doses up to 1 μM. Action potential duration at both 50% and 90% repolarization were decreased at 30 μM, potentially due to inhibition of the calcium current. The maximum rate of depolarization was reduced (at 10 μM) as was the amplitude, slightly, of the action potential (at 30 μM), an effect probably due to inhibition of the rapid sodium current.

At 0.25 Hz, Alfuzosin had no effect at doses up to 0.1 μM. No arrhythmias, no automatisms of the preparation, and no early afterdepolarizations of the action potential were observed. In addition to lengthening the final repolarizing phase of the action potential, Alfuzosin caused a lowering of the plateau of the action potential at 30 μM. These observations suggest that in addition to effects on the potassium currents, counterbalancing effects on the calcium current were observed. These effects were not completely reversed after a 30-minute washout.

Study title: Alfuzosin (SL77.0499-10): Effects on the HERG channel stably expressed in mammalian cell line. Comparison with tamulosin, doxazosin, prazosin and terazosin.

Key study findings: On HERG potassium current (I_{kr}), the Alfuzosin IC_{50} = 83.3 μM (35,500 ng/ml)(~2000 times the expected clinical blood level)

Study no: PGD0097
Four-month safety update, volume #25, and page #82
Conducting laboratory and location: Sanofi-synthelabo, Département de Pharmacologie Générale, 10, rue des Carrières, BP248, 92504 Rueil-Malmaison, France
Date of study initiation: 10 July 2000
GLP compliance: yes
QA reports: yes (x) no ( ):
Drug: batch # 0400.1A.02, 99.5% pure
Formulation/vehicle: standard extracellular medium

Methods: Using the whole cell patch clamp technique, the effect of Alfuzosin and reference compounds on the HERG current, stably expressed in CHO cells, was studied. N = 3-9 cells.

Dosing: 0, 0.01, 0.1, 1, 10, 100, and 1000 μmol/L

Results:

DRUG	IC_{50}
Alfuzosin	83.3 µmol/L
Tamsulosin	104.8 µmol/L
Prazosin	3.4 µmol/L
Terazosin	21.4 µmol/L
Doxazosin	2.5 µmol/L

Summary of individual study findings: Alfuzosin has less inhibitory effect on HERG potassium current (I_{kr}) than several other drugs in its therapeutic class.

Conclusions: Although evidence of effects on action potential were apparent using two frequencies of stimulation in Purkinje fibers, further investigation in CHO cells stably expressing HERG showed specific effects on potassium current (I_{kr}) to be present only at very high multiples of the clinical blood concentrations. (In addition, Alfuzosin is about 90 % protein bound in clinical blood samples, lowering the effective clinical exposure.) Effects on other ion channels have not been characterized. Human studies at 4 times the proposed clinical dose, however, have been conducted.

APPENDIX/ATTACHMENTS:

Attachment #1 12/22/97

Sponsor: Synthelabo Research, Secaucus, NJ 07094

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Review #1

DRUG: Alfuzosin Hydrochloride; N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl) methylamino] propyl] tetrahydro-2-furancarboxamide hydrochloride; SL77.0449-10

MF = $C_{19}H_{27}N_5O_4$ HCl MW = 389.5 (free base)

Formulation: 7.5, 10 or 15 mg sustained release Geomatrix oral tablets

Category: $Alpha_1$-Adrenergic antagonist

Indication: Benign Prostatic Hyperplasia (BPH)

TABLE OF CONTENTS

PHARMACOLOGY

Alfuzosin is a selective and specific antagonist of postsynaptic alpha$_1$-adrenoreceptors. Alfuzosin had little affinity for alpha$_2$-adrenoreceptors, and no affinity for dopaminergic, serotonergic, muscarinic, histaminergic or benzodiazepine receptors. Alfuzosin (3 mg/kg, iv) did not modify hypotensive responses to acetylcholine, histamine, or salbutamol. In addition, alfuzosin did not modify the tachycardiac effects of isoprenaline. Alfuzosin inhibits ^{3}H-prazosin binding to alpha$_1$-receptors in the rat cerebral cortex in vitro (IC_{50} = 0.0012 uM). The only metabolite of alfuzosin with affinity for a_1-adrenoreceptors is SL 80.0306-14 (4-fold less active than parent compound). All other metabolites of alfuzosin, including the primary metabolite SL 80.03630-69, are inactive. None of the metabolites of alfuzosin have significant affinity for a_2-adrenoreceptors. Both the R- and S- enantiomers of alfuzosin, SL 88.0054-10 and SL88.0053-10, are selective for a_1-receptors with affinity similar to that of the racemate. Both enantiomers are as potent as the racemate in inhibiting contractile responses of bladder trigone and urethral smooth muscle.

Alfuzosin is a uroselective a_1-antagonist which inhibits phenylephrine -induced urethral hypertonia at dose levels which have no effect on blood pressure. Alfuzosin (0.001 to 1 mg/kg, iv) inhibited phenylephrine-induced urethral hypertonia in cats at doses 3 fold lower than those required to produce the same level of inhibition of blood pressure. (UP_{50} = 0.031 mg/kg; MBP_{50} = 0.090 mg/kg).

Cardiovascular Effects

Alfuzosin, like other a_1-antagonists, reduces blood pressure in a dose-dependent manner. Following oral administration of 3 mg/kg alfuzosin, the maximum reductions in blood pressure were 60 mm Hg and 15 mm Hg in conscious SHR and normotensive rats, respectively. Alfuzosin (0.03 to 3 mg/kg, iv) caused dose-dependent decreases in systolic, diastolic and mean blood pressures in anesthetized normotensive dogs. At 3 mg/kg a 25% decrease in blood pressure was observed. At 10 mg/kg a 40% decrease in b.p was noted. In dogs, alfuzosin also produced decreases in heart rate at doses of 0.3 mg/kg, iv.

CNS Effects

Alfuzosin (10 mg/kg, po) produced no behavioral effects in mice in the Irwin screen. At 30 mg/kg, alfuzosin produced slight to moderate behavioral depression. Doses of 10, 30 and 100 mg/kg had no effects on rotorod performance in mice. Doses of 10, 30 and 100 mg/kg, po produced dose-dependent decreases in locomotor activity in rats.
Alfuzosin at dose levels from 10 to 100 mg/kg, po had no effects on hexobarbital-induced sleeping time in mice.

Respiratory Effects

Alfuzosin (10, 30, and 100 mg/kg, po) was administered to male guinea pigs and effects on respiration were monitored. Doses of 10 and 30 mg/kg decreased the inspiratory flow 22-23%. At 100 mg/kg, alfuzosin produced significant respiratory depression decreasing respiratory rate (-35%), inspiratory flow (-28%), increasing inspiration (+88%) and expiration (+44%) times and respiratory cycle duration (+60%).

Gastrointestinal Effects

Alfuzosin at dose levels of 1 and 3 mg/kg, po had no effect on GI motility in rats (charcoal meal transit time). Dose levels of 10, 30 and 100 mg/kg, po significantly inhibited gastric motility in male rats. Alfuzosin at dose levels of 5 and 10 mg/kg, po decreased gastric secretions 50-to 80% in female rats.

Renal Effects

Alfuzosin (10,30 and 100 mg/kg, po) reduced urine output in males rats. At the highest dose of 100 mg/kg, marked increases in electrolyte concentrations, increased urinary specific gravity, increased urinary protein concentration and lowered pH were also observed.

Endocrine Effects

Alfuzosin (10, 30, 100 mg/kg, po) had no effects on plasma testosterone levels of male rats. Disturbances in the estrus cycle were observed in female rats dosed with 30 and 100 mg/kg, po alfuzosin. In alfuzosin-treated female rats, marked increases in progesterone were observed at 100 mg/kg; dose-related increases in estrogen were observed at dose levels of 30 and 100 mg/kg.

PHARMACOKINETICS

One month oral toxicokinetic study in the rat with the compound alfuzosin. Synthelabo recherche, 1996.

PK studies were done in Sprague-Dawley rats following oral gavage doses of alfuzosin. There were 42 males and 21 females per dose group.

Day 1

Dose mg/kg/day	Sex	Cmax (ng/ml)	Tmax (h)	AUC0-24h (ng.h/ml)
5	M	36	3.0	239
	F	98	3.0	493
30	M	840	3.0	4208
	F	1834	3.0	7824
200	M	5018	3.0	47249
	F	6116	3.0	90332

Day 29

Dose mg/kg/day	Sex	Cmax (ng/ml)	Tmax (h)	AUC0-24h (ng.h/ml)
5	M	41	3.0	199
	F	112	0.5	447
30	M	890	3.0	4360
	F	2005	0.5	7960
200	M	8134	3.0	108855
	F	12599	3.0	156301

Toxicokinetics in rats during a one year study.

			DAY				
			1	7	89	180	362
	1 mg/kg	2h	2	5	5	6	6
		6h	trace	trace	1	trace	trace
MALE	5 mg/kg	2h	25	59	76	138	106
		6h	11	5	3	4	11
	25 mg/kg	2h	327	145	985	1070	830
		6h	72	58	29	34	124
	1 mg/kg	2h	8	17	20	29	21
		6h	1	trace	trace	trace	1
FEMALE	5 mg/kg	2h	26	85	177	221	188
		6h	16	5	10	7	21
	25 mg/kg	2h	415	543	1105	1586	1347
		6h	99	50	70	116	189

plasma concentrations are in ng/ml.
Sponsor states that 5 mg in humans gives blood alfuzosin concentrations of 17.8 ng/ml.

Evaluation of alfuzosin administered orally in the dog for 1 month as 7.5 mg tablets. Synthelabo Recherche, 1996.

Beagle dogs (3/sex) dosed once daily for one month 5 minutes after the end of the meal.

		Cmax (ng/ml)	Tmax (h)	AUC0-24h (ng.h/ml)
Male	Day 1	46	7.5	356
	Day 23	128	8.0	1156
Female	Day 1	77	8.0	764
	Day 23	42	8.0	522

The sponsor states that the delayed appearance of the compound in the plasma compartment was due to the delayed release from the Geomatrix tablet.

TOXICOLOGY

SINGLE DOSE

Species/strain	No. of animals (sex/group)	Dose/Route (mg/kg)	Approximate lethal dose	Symptoms
Mouse Swiss CD1	40 M + 40 F 60 M + 60 F 20 M + 20 F	1000, 1500, 3000 2000 4000/gavage	M: 2300 F: 1950	ptosis, sedation, motor disorders, piloerection, cyanosis, clonic convulsions
Mouse Swiss CD1	20 M + 20 F	400 - 1000/IP	M: 600 F: 650	ptosis, sedation, dyspnea, motor disorders, clonic convulsions
Rat Sprague Dawley CD	10 M + 10 F 20 M = 20 F	500, 1000, 2000, 4000/gavage	M: 4000 F: 3000	ptosis, motor disorders, bradypnea, sedation, red-stained tears, diarrhea
Rat Sprague Dawley CD	10 M + 10 F 20 M + 20 F	200 - 1300/IP	M: 480 F: 480	ptosis, hypotonia, diarrhea, bradypnea, clonic convulsion, cyanosis, sedation

Four Week Oral (in Diet) Dose-Finding Study in Mice, 83-00620-EN-00, [redacted] report # 3375-71/9

The study was conducted according to GLP by [redacted]

Crl:CD-1 BR mice (n = 9/sex/dose) were administered 0, 5, 20 and 30 mg/kg/day SL 77.499-10 in diet for 4 weeks.

Drug treatment produced no mortality, signs, or changes in body weight and food consumption. Hematology, clinical chemistry, urinalysis data were not obtained. Drug treatment had no effects on organ weights of the liver, kidneys or heart. Histopathologic evaluations were not performed. Toxicokinetics data were not provided.

Conclusion- Administration of alfuzosin at dose levels of 5, 20 and 30 mg/kg/day in diet produced no drug-related toxicity in mice.

Six Week Oral (in Diet) Dose Finding Study in Mice. 83-00619-EN-00; — # 82/ —3057/004 Lot # 11267

The study was performed at , from July 17, 1981 to September 2, 1981. There are no GLP assurance statements.

B6C3F$_1$ mice (n = 8/sex/dose) were administered 0, 100, 200 and 300 mg/kg/day in diet for six weeks. The 200 mg/kg group received 200 mkd for 4 weeks followed by 500 mkd for weeks 5 and 6.
Achieved doses- were within 10% of the desired value.

Mortality - none

Signs - ptosis was observed in the 300 mkd group during week 5 and in the group receiving 500 mkd for 2 weeks.

Body weight/food consumption; mean body weight was slightly increased in HD females (300 mkd) and LD males. Overall food consumption was slightly increased in all drug-treated groups. Since body weight changes did not display a dose-related pattern the relationship to drug treatment was unclear.

Water consumption - was assessed daily by visual inspection. Values were not measured and animals were grouped 4 per cage so no real information provided.

Hematology- (measured week 5)- unremarkable

Blood chemistry (measured week 6)- only AP, ALT, AST, Urea and triglyceride levels were measured. No drug-related effects

Organ weights-(only liver, spleen and kidneys were measured)
Liver- increased abs/rel wts in all treated female groups(wts in all treated groups were equivalent, maybe control values were low).
Spleen- increased abs/rel wt in 300 and 500 mkd females grps

Toxicokinetics- Blood samples were obtained one and four hours after lights on (7 and 10 am) after two weeks of dosing. Values were calculated from limited data (usually only two measurable samples), displayed large variability and did not display levels which were dose-related. There is no data provided on validation of the assay. The kinetics data is clearly inadequate to support dose selections for a carcinogenicity study.

Dose(mg/kg)	Mean Plasma SL77 499-10 (ng/ml) 7 am sample[a]	10 am sample[b]
Males		
100	144 (65-294)	43 (10-88)
200	85 (80-90)	20 (13-33)
300	258 (210-320)	96 (58-131)
500	216 (100-400)	nd
Females		
100	79 (73-84)	20 (10-36)
200	88 (60-130)	35 (10-54)
300	85 (60-130)	74 (49-99)
500	463(100-680)	nd

a. One hour after lights on.
b. Four hours after lights on.
nd - not determined

Gross pathology-
Spleen- swollen in 0 C, 2 LD, 4 MD (200 4 wks, 500 2 wks), 3 HD

Histopathology-(n = 8/sex/dose; only adrenals, liver and spleen were examined)

Adrenal-
cortical fatty vacuolization (slight)-0 males; 0 C, 4 LD, 3 MD, 3 HD F
cortical pallor- 1 C, 1 LD, 4 MD, 3 HD (both sexes combined)

Liver- ORO positive fat vacuolization- 0 M; 1 C, 2 LD, 2 MD, 4 HD F

Spleen- marked extramedullary hematopoiesis 2 C, 2 LD, 7 MD, 4 HD M; 2 MD females.

Summary and Conclusions-

B6C3F$_1$ mice were administered 0, 100, 200 and 300 mg/kg/day alfuzosin in diet for 6 weeks. The dose was increased to 500 mkd in the mid dose group for the last 2 weeks of the study.

There was no drug-related mortality, decrease in body weights or food consumption, or effects on hematology, blood chemistry or organ weights. Drug-related histologic changes included fatty vacuolization in the adrenal cortex and liver of female mice. Marked extramedullary hematopoiesis was also observed in the spleen of mid and high dose male mice.

No dose-limiting toxicity was observed in this study and the maximum tolerated dose was not determined. The study has many deficiencies including dosing for only 6 weeks, examination of a limited number of hematology and blood chemistry parameters, and organ weights and histopathologic evaluations for the adrenals, liver and spleen only. In addition, the toxicokinetics data are not of adequate quality (variable, plasma levels not related to dose, no Cmax or AUC data) to be used for dose selection.

Ninety-Eight Week Oral (Diet) Carcinogenicity Study in the Mouse. 86-0330-EN-00, Report #4592-71/5, lot # 11415

The study was conducted according to GLP by

CRL CD-1 mice (n = 51/sex/dose) were administered 0 (control 1 and 2), 10, 30 and 100 mg/kg/day alfuzosin orally in diet for 98 weeks. The study was conducted between 3-31-83 and 3-5-85. Twelve additional control and high dose (100 mkd) male mice were treated for measurement of plasma drug levels. Blood samples were taken at 7 am on day 2 and during weeks 13 and 26.

Mortality- The percent survival in the treatment groups are summarized in the table below. The study was terminated 4 weeks early due to the high mortality rate in the high dose males. The high dose of 100 mkd significantly reduced survival in males and therefore supports the concept that 100 mkd exceeded the MTD in male mice.

Percent Survival Week 98

	Control I	Control II	10 mg/kg/d	30 mg/kg/d	100mg/kg/d
Males	41%	53%	51%	49%	25%
Females	59%	46%	59%	63%	63%

Body weight/food consumption - drug treatment with alfuzosin at dose levels up to 100 mkd had no significant effects on mean body weights or food consumption.

Plasma drug levels- Plasma from 3 animals was pooled for determination of plasma levels of alfuzosin. Animals were sampled one hour after lights on (7 am). Actual data and/or SD were not provided.

	Alfuzosin (ng/ml)		
	Day 2	Week 13	Week 26
Males only	49	93	85

Organ weights- no drug-related effects on absolute organ weights in the liver, kidney, heart, gonads, adrenals, thyroid and spleen.

Histopathology- Administration of alfuzosin to mice for 98 weeks had no significant effects on the incidence of gross pathology, non-neoplastic pathology or neoplastic lesions.

Summary and Conclusions-
No significant increase in the incidence of non-neoplastic lesions or tumors was observed in mice treated with Alfuzosin at dose levels up to 100 mg/kg/day for 98 weeks. The high dose of

100 mkd exceeded the maximum tolerated dose in male mice since a significant increase in mortality was observed in this group. The adequacy of 100 mkd as the high dose in female mice was not established since no toxicity was observed with this dose level in the dose-finding or carcinogenicity study. Toxicokinetics data are inadequate to evaluate exposure comparisons to clinical doses or permit dose selections based on multiples of the AUC.

Recommendation- Data should be provided to the statistician for review. Synthelabo should also be required to conduct a toxicokinetics study in mice with the dose levels of alfuzosin utilized in the mouse carcinogenicity study (10, 30 and 100 mkd) designed to provided steady state pharmacokinetics data in mice.
The data obtained in female mice will allow assessment of the adequacy of the dose levels utilized in females (25 times human AUC ?).

Four Week Subacute Oral Toxicity in the Rat. 78-00295-EN-00, lot # 10723

The study was conducted by Synthelabo in 1978. No GLP or QA statements were provided.

Sprague Dawley CD rats (n = 12/sex/dose) were administered 0, 30, 100, 200 and 400 mg/kg/day orally by gavage (vehicle not specified) for 28 days.

Clinical signs: Slight and transient lethargy was seen early in the HMD and HD gp's. This disappeared after day 8 of treatment. Hypersalivation was sporadic in the HMD but was continuous in the HD. In males, slight and transient sedation occurred in the LMD but was marked and continuous in the HD during the first 2 wks of treatment. Thereafter, sedation regressed and ultimately disappeared during the final days of drug administration.

Mortality: No deaths.

Body wt: Body wt was markedly increased in treated females compared to controls. No significant effects were noted in males.

Food consumption: No differences between treated animals and controls.

Hematology: There was a slight decrease in Hb in HD females.
Slight but significant decrease in RBC count, hematocrit and Hb levels in treated males at all dose gps.
Slight decrease in leukocyte count in HD males.

Clinical chem: Slight increase in glucose in HD males and females.
Slight but significant increase in triglycerides in HD males.
Slight but significant decrease in total serum protein in HD females.

Urinalysis: An increase in urine volume was noted on day 24 in the HMD and HD gps.

Organ wts: Liver: Slight increase in wt in all dosed gps, with a marked increase in the HD gp for both sexes.
Spleen: Slight increase in LMD and HMD and a significant increase in the HD for both sexes.

Adrenals: Significant increase in HD males only.
Uterus: Slight decrease in all dosed females.
Seminal vesicles: Marked increase in the HMD and HD gps.

Gross path: Distended stomachs in HMD and HD females with substantive quantities of feces in the intestines of some animals. Slight thickening of urinary bladder in 7/12 HD females. In males, urinary bladder swollen with large amts of urine, especially for the HD animals.

Histology: Only the controls and HD animals were examined. In both sexes there was congestion of the spleen.
There were signs of thyroid gland activation in 7/12 males. This effect was not seen in females.
Seminal vesicle hypertrophy in males.

Assessment of toxicity to rats by repeated oral administration for 13 weeks. (80-00203-EN-00). [redacted] report # BGX 158-G/89439. 1980. Lot #

Sprague-Dawley CD rats were divided into 4 gps of 20/sex and were gavaged with alfuzosin in distilled water at doses of 0, 5, 30 or 200 mg/kg/day for 13 weeks. 16 rats/gp/sex were used for PK sampling.

Mortality: One death due to anesthesia.

Clinical signs: Bilateral ptosis was seen after the first dose and affected rats of both sexes in the MD and HD gps (occasionally seen in the LD gp). Frequency and severity did not decrease with time. Salivation affected all HD rats after week 5. Brown staining of the fur around the mouth was associated with the salivation.

Body wt: A slight but significant increase compared to controls was seen in HD females.

Food consumption: A significant but probably not drug related increase in LD males.

Water consumption: Increase in HD males.

Urinalysis: Increase in HD males at week 13 due probably to increase in water consumption.

Hematology: At wk 12 there was a significant reduction in PCV, Hb and RBC for HD females and a significant reduction in PVC in HD males. When examined on wk 13, HD females had decreased RBC values and both MD and HD males had decreased Hb and RBC values. However, values were within normal ranges and were considered by the sponsor to be of little toxicological importance.

Clinical chem: Slight changes which were not considered of toxicological significance.

Ophthalmoscopy: No effects.

Organ wts: Liver - significant increase in HD males and females.
Spleen - significant increase in MD and HD males.

Adrenal - significant increase in HD males.

Gross pathology: No treatment-related effects.

Histology: There was an increase incidence of moderate degree of hemosiderosis in HD rats which was more pronounced in males than females.

Toxicity in oral administration to rats for 26 weeks. (83-00355-EN-00). [redacted] # 82/[redacted]040/428, 1983. Batch no. 11 146.

Groups of 25 CD (remote Sprague-Dawley) rats/gp/sex were administered 0, 10, 50 or 250 mg/kg/day alfuzosin in distilled water by oral gavage for 26 weeks.

Clinical signs: From the first day of treatment "squinting" characterized by partial closure of the upper and lower eyelids was seen in nearly all treated rats. A dose-related incidence of peripheral vasodilatation (reddening of ears and paws) and red coloration of the eyelids was evident among treated rats from weeks 1 or 2. The incidence increased with time until week 5 when nearly all treated rats were affected.

These signs were observed as early as 30 minutes after dosing. In HD rats, squinting and red-rimmed eyes often persisted for up to 24 hrs after dosing while peripheral vasodilation persisted for up to 5 hrs after dosing.

Dilation of the vaginal opening was observed in some females from all treated gps, from the 10th day of treatment. By the end of the 5th week of treatment, the majority of females were affected.

Salivation was observed in HD rats. A few MD rats were affected after a wk of treatment.

From wk 7, a dose-related incidence of urogenital wetness was noted among MD and HD rats. The incidence was much reduced after wk 11. LD rats were unaffected.

Mortality: There was a dose-related increase in mortality in both male and females rats. Most died within 30 minutes of dosing and was frequently preceded by respiratory distress, cyanosis and excessive salivation. Others were found dead between 2 and 22 hrs after dosing. These animals exhibited usual reactions to dosing including squinting and peripheral vasodilation.

A range of unusual histopathological findings was present in the lungs of rats of this group, including congestion, multifocal desquamation of bronchiolar epithelium, focal thickening of the alveolar walls, perivascular edema, fragments of bronchiolar epithelium in the alveoli and focal fibrinous alveolar exudate.

Necropsy findings in rats of this gp were typified by the presence of aerated fluid in the trachea, prominent cervical lymph nodes, and pulmonary edema and congestion.

Food consumption: Slightly higher FC in LD and MD males and females and HD females.

Body weight: There was an increase bw gain of LD and MD rats and HD females. HD males had less bw gain than controls.

Ophthalmoscopy: The high incidence of squinting was confirmed at the Ophthalmoscopic exam. No positive evidence of fear of light or light avoidance could be elicited.

Hematology: Changes indicating possible mild macrocytosis in LD and MD females and in HD males and females. In support, the myeloid:erythroid ratios in the bone marrow of these animals showed a slightly higher proportion of animals in these gps with increases in the erythroid series when compared to controls. These differences were small with questionable toxicological significance.

Clinical chem: Increase in plasma triglyceride concentrations in MD males and MD and HD males and females. Serum calcium was lower in HD animals than controls.

Urinalysis: No apparent treatment-related effects.

Organ wts: Relative (to body wt) liver wts were increased in MD and HD males and in HD females. Absolute and relative adrenal wts of HD males were increased from controls and there was a trend in MD males. Absolute and relative spleen wts of MD and HD males and females were higher than controls.

Absolute and relative uterine wts of MD and HD females were lower than controls but these gps ovaries were heavier than controls.

Absolute prostate wt in MD and HD males was lower than controls.

Gross pathology:
Animals dying or killed prematurely during the treatment period: The majority of animals dying or killed in extremis were HD animals. A range of lesions was present in these animals which were similar in type and incidence to those commonly found in rats at
These included pulmonary edema and congestion and prominent cervical lymph nodes. However, frothy exudate was apparent in the trachea and nasal and oral staining was evident, and these are unusual findings.

Animals killed after 26 wks of treatment: No unusual findings.

Histopathology: There was enlarged pale, foamy cells of the adrenal zona glomerulosa in MD males and HD males and females. There were significant effects on the liver. At the MD there was periacinar cell shrinkage necrosis and at the HD there was cytoplasmic eosinophilia, periacinar accumulations of brown pigment, periacinar cell shrinkage necrosis and periacinar eosinophilic cytoplasmic bodies in males, and panacinar hepatocytic glycogen pallor, clear cell foci, periacinar accumulations of brown pigment and periacinar cell shrinkage necrosis in females.

In HD females, there was an increased incidence of slight acinar hyperplasia and secretion in the mammary glands and reduced uterine size. In HD males, there was reduced secretion of the

prostate. In LD males there was reduced secretion of the prostate, and possibly some enlarged, pale foamy cells of the adrenals.

There were significant effects in the lungs of all premature decedents (including controls). The HD group had a high incidence of multi-focal desquamation of bronchiolar epithelium, fragments of the bronchiolar epithelium in alveoli, perivascular edema and congestion and thickening of alveolar walls. These findings were consistent with the signs of respiratory distress seen before death in many of the premature decedents receiving the HD and the increased lung wts in HD animals. The most likely cause of death was hypotensive shock,

Toxicity assessment of alfuzosin administered orally to rats over a period of one year. 91-00327-EN-00, Synthelabo Research, 1991.

Twenty Crl:CD(SD)BR (Sprague-Dawley) rats were gavaged with 1, 5 and 25 mg/kg alfuzosin. Twenty-four/sex/gp were treated similarly and used for toxicokinetic measurements.

Mortality: No controls died. There were 2 deaths in the LD and 5 in the MD and HD. The sponsors state that 1 LD, 3 MD and 2 HD deaths were not explained by technical errors.

Clinical signs: Mild palpebral ptosis at two higher doses. Scrotal reddening or vaginal dilatation at all doses. In the animals that died, symptoms included hypomotility, apnea, swelling, tremor, soft feces, red nasal discharge and red urine, posterior paresis, ocular discharge, mucosal pallor and bodyweight loss.

Body weight: Some increase in wt gain, particularly HD females during the first 5 months of the study. HD females weighted 6% more than controls at the end of the study.

Food consumption: Increase, particularly in HD. 7% for males and 5% for females.

Electrocardiographic findings: ECG's were recorded between 0.5 and 1 hr after drug administration at months 6 and 12. There was a slight increase in heart rate at all doses. This was statistically significant for HD males at 6 months (29%) and HD females at 12 months (20%). There was a parallel increase in the QTc interval (corrected for heart rate; males +24%, females +13%). There was 2nd degree atrio-ventricular block in one HD female at 12 months.

Blood pressure: Systolic arterial pressure was measured under the same conditions as the ECG. There was a significant decrease in BP of 22% in M and F at 6 months and a decrease of 14 to 36% in M and F at 12 months.

Ophthalmology: No treatment related effects.

Hematology: There were changes in the MD and HD but all values were within laboratory limits.

Clinical chem: No significant treatment related changes.

Urinalysis: No toxicologically significant changes.

Organ weights: Changes affected HD animals only (except thyroid). There were statistically significant increases in liver, rel wt in F and abs wt in M. Kidney, abs/rel in M. Spleen abs/rel in M and abs in F. Thyroid, abs/rel in HD M and abs in MD M. Pituitary, abs in F.

Gross pathology: No treatment related effects.

Histopathology: No treatment related effects.

Toxicokinetics:

			DAY				
			1	7	89	180	362
	1 mg/kg	2h	2	5	5	6	6
		6h	trace	trace	1	trace	trace
MALE	5 mg/kg	2h	25	59	76	138	106
		6h	11	5	3	4	11
	25 mg/kg	2h	327	145	985	1070	830
		6h	72	58	29	34	124
	1 mg/kg	2h	8	17	20	29	21
		6h	1	trace	trace	trace	1
FEMALE	5 mg/kg	2h	26	85	177	221	188
		6h	16	5	10	7	21
	25 mg/kg	2h	415	543	1105	1586	1347
		6h	99	50	70	116	189

plasma concentrations are in ng/ml.
Sponsor states that 5 mg in humans gives blood alfuzosin concentrations of 17.8 ng/ml.

Four Week Range Finding Dietary Study in Rats. 82-00071-EN-00, lot # 11267
[redacted] report # 81/ 056/498; [redacted] 1982.

Groups of 10 Sprague-Dawley CD rats/sex were given 100, 200, or 300 mg/kg/day of alfuzosin in the diet for 4 weeks. Satellite groups of 5/sex were used for blood collection.

Clinical signs: Squinting (partial closure of both upper and lower eyelids) was seen in all treated rats on the morning following the first day of treatment and persisted throughout treatment. No increase in severity occurred during treatment and the degree of squinting was not dose related. Peripheral dilation (slight reddening and hyperthermia of the ears and extremities of the limbs) was seen in male HD rats. Vaginal dilation was seen in 4 MD and all HD females and was progressive in terms of incidence and degree.

Mortality: One female HD rat in the satellite group was sacrificed moribund. Cause of death was not determined.

Food consumption: No treatment related effect.

Bodyweight: No effect.

Ophthalmoscopy: Dose-related slitting of the eyes.

Hematology: Slight decrease in pcv, hgb conc and rbc count from controls , particularly in females in all treatment gps. Basically, no meaningful, treatment-related effects.

Clin chem: Possible treatment-related decrease in liver enzymes (AST in MD and HD females and ALT in all treated rats). HD males had increase in plasma triglycerides.

Organ wts: Slight increase in spleen wt in all treated gps.

Gross path: Treatment related vaginal dilation in MD and HD females.

Histopath: In livers of MD and HD males, there was an increased incidence of slight and moderate panacinar (glycogen) pallor.

104 Week Oral (Dietary Administration) Carcinogenicity Study in the Rat. 85-00665-EN-00, [redacted] 1985.

Five groups of 50/sex Crl:CD(SD)BR rats were given 10, 30 or 100 mg/kg/day alfuzosin in the diet. There were two separate control groups.

Clinical signs: No treatment-related signs.

Mortality: No treatment-related effect.

Body wts: There was a treatment-related reduction in bodyweights compared to control beginning by wk 26 in HD males and by week 52 in HD females. Body wt depression of approximately 8-13% compared with controls were observed at study termination. No effects were seen in the MD or LD. Final body wts for males were control 1; 743, control 2; 706, LD: 737, MD; 717, HD; 653. For females the results were control 1: 488, control 2; 496, LD; 477, MD; 509, HD; 433.

Food consumption: A reduction in fc compared with control was seen by wk 26 in HD males and by week 52 in HD females. Food consumption in HD males was depressed by 10% during the second half of the study, compared with controls, paralleling the reduction in body wts. Sponsor claims that the decreased fc was not the result of poor drug palatability.

Organ wts: There was an increase in absolute and relative liver wts in MD and HD males and in HD females.

Gross path: No treatment-related effects.

Histopath: There were no significant treatment related effects in non-tumor histology. The tumor profile was mainly endocrine with pituitary and mammary gland tumors most prevalent. The sponsor states that there was no treatment-related increase in tumor incidence.

Four Week Oral Toxicity Study in Beagle Dog. 79-00309-00.

Two dogs/sex/gp were given gelatin capsules of 0, 50, 100 and 200 mg/kg/day of alfuzosin.

Mortality: Two high dose dogs.

Clinical signs: On each study day, every treated dog showed marked bilateral palpebral ptosis, somnolence during the hrs following drug administration, and muscular tremors and motor incoordination of the hindquarters.

Bodyweight: By the end of the study, 3 of 4 high-dose dogs had a 25% decrease in body weight compared to controls.

Food consumption: Retarded in all treated animals but 2 HD animals stopped eating their entire daily ration.

Electrocardiograms: There was a decrease in heart rate in HD dogs after 4 weeks of treatment.

Ophthalmoscopy: No treatment related effects (only control and HD examined).

Hematology: No significant effects.

Clinical chem: In one high-dose female, there was an increase in transaminases (especially SGPT) and cholesterol was reduced.

Macroscopic exam: There was blood in cecum of one MD dog. In the HD dogs that died, there was pale and enlarged kidneys, thick walls and hemorrhagic stomach, congested intestines, white deposits in bladder, marked biliary stasis, red spots in lungs, and stasis in spleen. One dog was normal and the other had moderately discolored kidneys and stasis of spleen.

Organ weights: No significant differences.

Histopathology: Only clear effects were in the kidney. Including focal interstitial edema, diffuse interstitial and epithelial nephritis, marked focal dilation of the tubules and focal tubular nephrosis.

Oral toxicity study in beagle dogs. Repeated dosage for 13 weeks. 80-00692-EN-00. 1980.

Three beagles/sex were given 0, 5, 20 and 80 mg/kg/day alfuzosin in gelatin capsules.

Mortality: None

Clinical signs: Dose related increase in abnormally soft feces, vomiting, peripheral vasodilatation, abnormal quietness, extension of the nictitating membranes, generalized fine muscular tremors and excessive salivation.

Bodyweight: No treatment effects.

Food consumption: No effect

Ophthalmoscopy: Extension of the nictitating membrane in a majority of treated animals in the exam performed at week 12. No other effects.

Electrocardiography: There was a slight decrease in heart rate in HD animals.

Hematology: No significant treatment related effects.

Clinical chem: Increase in serum creatinine in HD animals.

Urinalysis: No significant treatment related effects.

Macroscopic findings: No abnormalities.

Organ weights: Possible increase in adrenal and pituitary wts in HD dogs.

Histology: No effect noted in adrenal or pituitary. No treatment-related changes were detected.

Fifty-three week oral toxicity study in beagle dogs with interim sacrifice at 26 weeks. 83-00616-EN-00. [redacted] # 82, 041/399.

Groups of seven beagle dogs/sex received alfuzosin in gelatin capsules at doses of 5, 20 or 80 mg/kg/day for at least 53 weeks. A control gp received empty capsules. After 26 wks, 3/sex were sacrificed.

Mortality: None treatment-related

Clinical signs: There was protrusion of the third eyelid, photophobia, conjunctivitis, subdued behavior, muscle tremors, nasal dryness, loose stools, and reduced incidence of estrus. These signs were generally seen from 30 min to 6 hrs after dosing, but were usually gone by the next morning.

Body weight: High dose females had a marginal decrease in wt gain from wk 2 to wk 26, after that bw gain was normal.

Ophthalmoscopy: Photophobia (narrowing of the eyelids, constricted pupils and evidence of discomfort), usually associated with conjunctivitis and protrusion of the third eyelid was seen in MD and HD dogs of both sexes and also in LD females.

Electrocardiography: No treatment related effects.

Hematology; No treatment related effects.

Clinical chem: No treatment related effects

Urinalysis: There was an increase in blood pigments during the first 24 weeks of treatment in MD and HD dogs. Thereafter, no effect was seen.

Organ weights: Decrease in uterine weight by 26 weeks in MD and HD females. No other treatment related effects.

Macroscopic pathology: No treatment related effects.

Histopathology: Interim sacrifice: In the liver, there was a slight enlargement of centriacinar hepatocytes in a HD male and female.

Terminal sacrifice: The ovaries of 3 MD and 2 HD females showed a suppression of follicular maturation and ovulation. There was an absence of corpora lutea and a degeneration of secondary follicles in these ovaries. The related genital tracts were in the anestrus state. No apparent effect on the liver was noted.

REPROTOXICOLOGY

Effects of oral administration upon reproductive function in the rat. Dosage range finding study. [redacted] 80-00154-EN-00, 1980.

[redacted] (Sprague-Dawley origin) rats were given by oral gavage 100, 200 and 250 mg/kg/day alfuzosin. There were 6 rats/sex dosed for 15 day prior to and throughout mating, gestation and lactation to day 4 post partum.

Results: Lethargy and partial closure of eyes occurred in all treated gps (greater at the two higher doses). Bodyweight gain was increased in females. Weight gain of females during gestation was slightly reduced up to day 14 in the MD and HD gps. But then improved and was greater than controls.

There were extended periods of diestrus (this was interpreted to be a condition of recurring pseudo-pregnancy) and pre-coital intervals in the MD and HD females.

Survival of offspring to day 4 post partum was reduced at the HD due mainly to total loss of 3/5 litters. Dead offspring generally had no milk in their stomachs.

The sponsor concluded that the highest dose of alfuzosin should be less than 200 mg/kg/day.

Effects of oral administration upon reproductive function and fertility in the rat. 81-00845-EN-00. [redacted] 1981.

F_0 generation

CD (Sprague-Dawley origin) rats (26/sex/gp) were gavaged with 0, 5, 25 and 125 mg/kg alfuzosin. Males were dosed for 71 days before pairing, throughout the mating period until successful mating had been achieved. Females were dosed for 15 days before pairing, throughout the mating period, gestation and lactation until weaning on day 25 post partum. Males and females from the same treatment gp were mated.

General condition and mortality: No mortality. Following drug administration there was ptosis and slight lethargy which regressed within 24 hrs except for HD females where the effect persisted until the next dose for the first 2 weeks and thereafter regressed within 24 hrs.

Bodyweight: There was an increase in bw in both males (HD) and females (MD, HD) which returned to normal during the study.

Estrus cycle: Some MD and most HD females were acyclic or exhibited irregular cycles.

Mating performance and fertility: No treatment related adverse effects on mating performance, conception rate or fertility.

Litter responses

Females killed on day 21 of gestation: No treatment related effects

Females allowed to litter: Slight increase in gestation length in HD. Viability in HD gp was slightly reduced, resulting in a slight reduction in mean litter size at weaning.

Terminal studies: One incidence of hydrocephaly and one incidence of cleft palate in HD. One incidence of hydrocephaly in MD.

F_1 Generation: No treatment related effects.

Conclusion: Drug administration of 5 mg/kg and above was associated with ptosis and lethargy. Doses of 25 and 125 mg/kg were associated with an increased length of estrus cycle and the majority of HD females were acyclic or had irregular estrus cycles, but reproductive performance was unaffected. No significant effects on fertility or effects on subsequent generations were noted.

Fetal toxicity in the female rat. Oral route. 78-00317-EN-00. Synthelabo, Study done in 1978, report dated 1996.

Female CD rats (20/gp) were given alfuzosin by gavage from day 6 to day 15 of gestation. Doses were 100, 200 and 400 mg/kg.

HD animals experienced transitory phases of lethargy with ptosis and hypersalivation. There was reduced weight gain in HD females.

Fetal toxicity: Number of fetuses/litter and fetal weights were normal.

Abnormalities: All fetuses were examined macroscopically. Approximately 57 fetuses from the controls and high dose were examined microscopically for visceral and skeletal malformations. There was an increased incidence of absence of sternebrae (11/58 vs 30/57) and retardation of ossification (17/58 vs 44/57) in treated pups compared to the controls.

Effects of oral administration upon pregnancy in the rat. 80-00352-EN-00, ——— ——— , 1980.

Twenty female CD rats/gp were gavaged with 10, 50 and 250 mg/kg alfuzosin from day 6 to day 15 of gestation.

Clinical signs: MD and HD showed resistance to dosing and HD animals had some facial staining and dorsal hair loss. All treated females showed slight lethargy and partly-closed eyes after dosing.

Bodyweight: Significant increase in bw gain in HD.

Terminal studies:

Maternal observations: No effects

Litter responses: No adverse effects on numbers of implantations, pre- and post-implantation losses and viable young, and fetal and placental weights.

Fetal evaluation: All fetuses were examined macroscopically. Two thirds of each litter were examined by the Dawson staining technique (?) for skeletal malformations. The remaining third were examined for visceral malformations using the Wilson technique.

No consistent treatment or dose related effects were noted.

Effects of oral administration upon pregnancy in the rabbit. 80-00221-EN-00, ——— ——— . 1980.

Alfuzosin was administered by gavage to 14-15 New Zealand White Rabbits/gp from day 6 to day 18 of pregnancy at doses of 10, 30 and 100 mg/kg/day.
A preliminary study (80-00217-EN-00) demonstrated that 250 mg/kg resulted in 3 deaths out of 4 animals, with fur loss, emaciation and inactivity but with no obvious pathology at necropsy.

Maternal response:

General condition and mortality: No treatment related deaths. No other effects.

Bodyweight: Weight gain was significantly lower in the MD and HD during treatment but subsequent weight gain was similar or slightly greater than controls.

Litter response:

No effect on numbers of implantations and viable young, pre implantation loss and mean fetal and placental weight. An increase in post implantation loss was not significant and was within historical control range.

Fetal evaluation: There was an increased incidence of small fetuses in the HD gp. Following skeletal exam there was two LD and 2 MD malformations. Since no malformations occurred at the high dose and since similar findings had been seen in this rabbit strain, these findings were not considered treatment related.

Effects upon peri- and post-natal development in the rat. 80-00153-EN-00. [redacted] 1980.

Twenty CD (Sprague-Dawley origin) rats/gp were gavaged with 5, 25 and 125 mg/kg alfuzosin from day 15 post coitum until day 21 post partum.

Maternal observations:

General Condition: No effects except for the pharmacological response of ptosis seen in all treated gps.

Body weight: Slight decrease in bw gain during lactation in MD and HD gps but not dose related.

Gestation length: Marginal increase in gestation length in MD and significant increase in HD. No parturition problems and normal gestation index.

Litter observations

General condition: No treatment related effects.

Litter size: No effects

Body weight: Increase bw in HD pups on days 1 and 4 probably due to increased length of gestation.

Sex ratio: No effects

Physical development: No effects.

Terminal exam: No macroscopic findings were noted.

GENOTOXICOLOGY

Mutagenicity test using Salmonella HIS. 79-00004-EN-00. Synthelabo, 1984. Report dated 1996.